EDI200

PROTOCOL NUMBER ECP-002

A PHASE 2 OPEN-LABEL, DOSE-ESCALATION STUDY TO EVALUATE THE SAFETY, PHARMACOKINETICS, IMMUNOGENICITY AND PHARMACODYNAMICS/EFFICACY OF EDI200, AN EDA-A1 REPLACEMENT PROTEIN, ADMINISTERED TO MALE INFANTS WITH X-LINKED HYPOHIDROTIC ECTODERMAL DYSPLASIA (XLHED)

Investigational Product:	EDI200
Development Phase:	Phase 2
IND Number:	109262
EudraCT Number:	2012-003561-17
Protocol Number:	ECP-002
Indication Studied:	Treatment of X-Linked Hypohidrotic Ectodermal Dysplasia in Infants with EDI200
Sponsor:	Edimer Pharmaceuticals, Inc. 55 Cambridge Parkway, Suite 102W Cambridge, MA, USA 02142
Study Initiation Date:	16 Sep 2013
Study Completion Date:	28 Sep 2015
Release Date of Report:	31 May 2016
Sponsor Contact:	Neil Kirby, Ph.D. President & CEO Edimer Pharmaceuticals, Inc. Tel: 617-230-0093 Fax: 866-334-4240 Email: neil@edimerpharma.com

This trial was conducted in accordance with the ethical principles of Good Clinical Practice, according to the International Conference on Harmonization Harmonized Tripartite Guideline.

STUDY TITLE:

A Phase 2 open-label, dose-escalation study to evaluate the safety, pharmacokinetics, immunogenicity and pharmacodynamics/efficacy of EDI200, an EDA-A1 replacement protein, administered to male infants with X-Linked Hypohidrotic Ectodermal Dysplasia (XLHED)

SIGNATURES:

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Edimer Pharmaceuticals Inc.

Neil Kirby, PhD
President & CEO — 31st May 2016 (Date)

CTI Clinical Trial and Consulting Services

Tom Winrod
Associate Director, Clinical Operations — 31MAY2016 (Date)

William Aronstein, PhD, MD, FACP
Vice President, Medical Affairs — 03 JUN 2016 (Date)

David McCollum, MS
Director, Biostatistics — 31 May 2016 (Date)

Dave Facklam
Senior Director, Regulatory & Scientific Affairs — 01 Jun 2016 (Date)

2. SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
Edimer Pharmaceuticals, Inc.</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier
Volume:
Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
EDI200</td></tr>
<tr><td>Name of Active Ingredient:
EDI200</td></tr>
<tr><td colspan="3">Title of Study:
A Phase 2 open-label, dose-escalation study to evaluate the safety, pharmacokinetics, immunogenicity and pharmacodynamics/efficacy of EDI200, an EDA-A1 replacement protein, administered to male infants with X-Linked Hypohidrotic Ectodermal Dysplasia (XLHED)</td></tr>
<tr><td colspan="3">Principal Investigator (PIs):
Holm Schneider, MD
Prof Angus Clarke, DM FRCP
Dorothy Grange, MD
Christine Bodemer, MD, PhD
Ophir Klein, MD
Pranoot Tanpaiboon, MD</td></tr>
<tr><td colspan="3">Study centers:
University Hospital Erlangen Nurnberg
Cardiff University School of Medicine
Washington University School of Medicine
CHU Paris - Hôpital Necker-Enfants Malades
University of California, San Francisco
Children’s National Medical Center</td></tr>
<tr><td colspan="2">Studied period (years):
Date first patient enrolled: 16 Sep 2013
Date last patient completed: 28 Sep 2015</td><td>Phase of development:
2</td></tr>
<tr><td colspan="3">Objectives:
Primary:
To assess the safety, pharmacokinetics (PK) and immunogenicity of EDI200 administered to XLHED-affected neonates
Pharmacodynamic/Efficacy:
To assess the pharmacodynamics/efficacy of EDI200 administered to XLHED-affected neonates
To compare clinical data and medical history obtained from untreated male siblings to that of the XLHED-affected neonates receiving study drug</td></tr>
<tr><td colspan="3">Methodology:
Phase 2 open-label, three cohort, dose-escalation study</td></tr>
</table>

Number of patients (planned and analyzed): 9-15 XLHED-affected male neonates for study drug administration
Diagnosis and main criteria for inclusion: Male neonates documented by genetic diagnosis to carry an Ectodysplasin A (EDA) mutation associated with XLHED
Test product, dose and mode of administration, batch number: 3, 10, or 20 mg/kg/dose administered intravenously (IV) Batch Numbers used in this study: 1-FIN-1172 and 12-085-001
Duration of treatment: Subjects received a total of 5 doses over 15 days
Criteria for Evaluation: Pharmacodynamic/Efficacy Evaluations: • Growth and development • Infections and hospitalizations • Dentition • Facial development • Sweat gland number and function • Dry eye assessment • Thermoregulation • Skin biopsy for expression profile Safety Evaluations: • Safety laboratory blood tests • Vital Signs • Adverse Events (AEs) Pharmacokinetics Evaluations: • Serial blood draws
SUMMARY – CONCLUSIONS **SAFETY RESULTS:** Overall, EDI200 was generally well tolerated, and the development of anti-drug antibodies (ADA) was not seen in any of the 10 subjects. No significant actions were taken with EDI200 for safety reasons. No safety risks of EDI200 were identified that would have required major changes to the design of the completed clinical study, to the doses that were administered, or to the clinical development plan for EDI200. **CONCLUSION:** This trial was a first-in-neonate, open-label, multicenter Phase 2 dose-escalation study of EDI200 administered to XLHED-affected infants. Its design incorporated the experience gained from the previously complete adult study. The study successfully met its goals of enrolling 3 cohorts and completing the planned course of 5 IV doses in every one of the 10 subjects. Data Safety Monitoring Board (DSMB) involvement and review of the Phase 2 study results contributed to the determination of final parameters for study treatment doses and monitoring in this study. The primary objectives of demonstrating safety and determining immunogenicity and PK were met. Immunogenicity was

measured by the presence or absence of ADA in the serum. All subjects enrolled into the 3 cohorts and dosing with EDI200 had negative ADA results.

Date of the report:
31 May 2016

3. TABLE OF CONTENTS FOR THE INDIVIDUAL CLINICAL STUDY REPORT

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation or specialist term	Explanation
AE	Adverse Event
ADA	Anti-drug antibody
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DOL	Day of Life
DSMB	Data Safety Monitoring Board
EDA	Ectodysplasin A
EDA-A1	Ectodysplasin-A1
EDAR	Ectodysplasin-A1 Receptor
eNO	Exhaled Nitric Oxide
IV	Intravenous
PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetic
PT	Preferred Term
RSV	Respiratory syncytial virus
SAE	Serious Adverse Event
SOC	System Organ Class
TD	Treatment Day
TEAE	Treatment-emergent Adverse Event
TESAE	Treatment-emergent Serious Adverse Event
Wt	Weight
XLHED	X-Linked Hypohidrotic Ectodermal Dysplasia

9. INVESTIGATIONAL PLAN

9.1. Overall Study Design and Plan: Description

This was a first-in-neonate, open-label, multicenter Phase 2 dose-escalation study to evaluate the safety, pharmacokinetics (PK), immunogenicity, and pharmacodynamics/efficacy of EDI200, an Ectodysplasin A1 (EDA-A1) replacement protein, administered to male and female infants with X-Linked Hypohidrotic Ectodermal Dysplasia (XLHED). Dose-escalation in XLHED neonate cohorts did not occur until a review of safety and PK data from prior XLHED neonate cohorts was completed by the Data Safety Monitoring Board (DSMB), approximately 3 weeks after the last subject was dosed in each previous cohort. In addition, the DSMB also met to review data for each subject after the dosing period was completed and had at least 1 week of follow-up before the subsequent subject was dosed. The DSMB is detailed further in Section 9.2.

An estimated total of 9-15 XLHED-affected male neonates 48 hours to 2 weeks of age with genetic confirmation of XLHED diagnosis were expected to be enrolled into 3 cohorts and receive EDI200. In the US, UK, and France, the study was limited to only male subjects. In Germany, the study allowed for enrollment of male and female subjects. The sample size is based on clinical and practical considerations for a Phase 2 study in an ultra-rare genetic disorder with enrollment limited to newborns.

Subjects were enrolled sequentially into either cohort 1, 2, or 3 and were to receive a 3 mg/kg, 10 mg/kg, and 20 mg/kg dose of EDI200 administered intravenously on Days 0, 4, 7, 11, and 14, respectively. Vitals signs were monitored during EDI200 infusion and for 24 hours following each dose of study drug. Final cohort size was determined by subject and site availability, with at least 3 subjects per cohort. An independent DSMB was established to monitor the safety of the treated subjects prior to dose escalation. After completion of dosing in cohort 1, the DSMB was to meet and review the safety and PK data from all cohort 1 subjects prior to initiation of dosing in cohort 2. After completion of cohort 2 dosing, the Sponsor was allowed to elect to enroll into cohort 3 with EDI200 at a dose of 20 mg/kg. Prior to initiation of cohort 3, the DSMB was to review the safety and PK data from cohorts 1 and 2 and provide guidance on dose escalation to the higher level.

Study duration for each subject receiving study drug was approximately 6 months, including a treatment and safety/efficacy monitoring period, with all subjects rolling over into a long-term extension study providing yearly evaluations. The Schedule of Assessments are presented in Table 2 and Table 3.

In addition to the core study, all affected and unaffected male siblings, including multiple male siblings of a single neonate, of enrolled XLHED-affected neonate subjects were offered the opportunity to participate in a non-treatment, non-invasive evaluation providing historical control data for this open-label study. The sibling sub-study technologies involved were modeled on the core study evaluations with the exception that no X-rays were taken and no blood draws nor tissue sampling were involved. The evaluations took place at the study site and included Informed Consent and Assent, if applicable, medical history, physical examination, vital signs, including weight and height, digital facial photographs (frontal and lateral), growth and development assessments, induced sweating and sweat duct imaging, pulmonary function testing and exhaled Nitric Oxide (eNO) levels when age-appropriate, dry eye evaluation, and dental

examination. Siblings were asked to provide copies of their most recent dental radiographs. Expected stay at the study site location, i.e. within the vicinity of the study site, was 1-2 days.

The full protocol and all amendments are provided in Appendix 16.1.1, and a sample case report form (CRF) is provided in Appendix 16.1.2.

9.2. Data Safety Monitoring Board

A DSMB was responsible for safeguarding the interests of trial participants, for assessing the safety of interventions during the trial, and for monitoring the overall conduct of the clinical trial The DSMB provided recommendations on stopping or continuing the trial, as well as cohort dose escalation based on safety and exposure results.

The DSMB conducted a safety review after each newborn subject had completed the dosing period and had been followed for 1 to 2 weeks. At each meeting, the DSMB had an opportunity to review data, speak with the Principal Investigator (PI) at the enrolling site, and ask questions. During the closed session, the DSMB would discuss whether dosing of the next subject in that cohort should be recommended. In every instance, the Board recommended proceeding with the next subject.

In addition, the DSMB conducted a formal safety, tolerability, and PK data review following the dosing of all subjects in cohort 1 to inform dose escalation in cohort 2. The cohort 1 PK data review was intended to confirm both the EDI200 exposure levels, in the cohort as a whole and for each subject, were within the safe limits associated with study drug administration in preclinical Good Laboratory Practice toxicology studies, and the expected exposure of dose escalation in cohort 2 would remain in the range that was safe and well tolerated. Prior to the dosing of neonates in cohort 2, the DSMB also reviewed the safety and PK data from XLHED-affected adult cohort 2 subjects, who were also dosed with 10 mg/kg/dose for the same 5-dose regimen. Though adult data for the 20 mg/kg cohort (cohort 3) was not available, the same process described above was followed prior to dose escalation to cohort 3.

Details are provided in the DSMB Charter in Appendix 16.4.

Table 2: Schedule of Assessments – Multi-dose EDI200 Administration

	Screening		**Baseline**	**Treatment Phase**									**Follow-up Visits**	**Study Completion**
	Prenatal[1] (Optional)	Postnatal[2] DOL 2 to DOL 12	DOL 2 to DOL 14[3]	TD 0	TD 1	TD 2	TD 4	TD 7	TD 11	TD 14	TD 15	TD 16	TD 21	Mon 2 & 4 of Life[4] (±1 week)	Mon 6 of Life[4] (± 2 weeks)
Informed Consent	X	X	X												
Inclusion/Exclusion	X	X	X												
Genetic testing			X[5]												
Medical History	X	X[6]	X												
Safety Evaluations															
Physical Examination[7]			X	X	X		X	X	X	X	X		X	X	X
Safety Laboratory			X		X							X	X	X[8]	X
Immunogenicity			X									X		X[8]	X
Pharmacokinetic[9]			X	X	X	X				X		X	X	X[8]	X
PD/Efficacy															
Growth/Development			X											X	X
Dentition[10]			X												
Facial Development[11]			X												X
Sweat Assessments			X											X[8]	X
Dry eye Assessment			X												X
Thermoregulation[12]			X										X		
Skin biopsy sample			X		X						X				
Study Drug				X			X	X	X	X					
Adverse Events/Con Meds[13]	X														

Abbreviations: DOL = Day of life; PD = pharmacodynamics; TD = Treatment Day.

Table 3: Schedule of Assessments – Male Siblings of Study Subjects

	Study Enrollment	Evaluation
	From date of 1st dose study drug administered to affected sibling	Prior to Study Completion for affected sibling
Informed Consent	X	
Inclusion/Exclusion Criteria	X	
Medical History	X	
Safety Evaluations		
Physical Examination		X
Weight, Height, Vital Signs		X
XLHED-associated Outcomes		
Growth/Development Assessment		X
Infections/Hospitalizations		X
Dentition		X[14]
Facial Development		X[15]
Sweat Assessments		X
Pulmonary function[16]		X
eNO level[17]		X
Dry eye Assessment[18]		X
Adverse Events & Con Meds	X	

Abbreviations: DOL = Day of life; EDA = Ectodysplasin A; EDAR = Ectodysplasin-A1 Receptor; eNO = exhaled Nitric Oxide; PD = pharmacodynamics; PK = pharmacokinetic; TDs = Treatment Days.

Notes for Tables 2 and 3:

1. Optional prenatal screening enrollment is from end of first trimester through delivery date.
2. Newborn's screening window for study inclusion is through DOL #12.
3. Baseline evaluations must be completed by DOL #14.
4. Follow-up visits at 2, 4 and 6 months of chronologic age.

5. In the Screening process, confirmation of subject Ectodysplasin A (EDA) genotype is required from the family. Under Baseline Events, Ectodysplasin-A1 Receptor (EDAR) genotyping for the phenotype-modifying polymorphism EDAR V370A will be a standard assessment (Cluzeau et al., 2012) but is not required prior to study drug administration.
6. Medical history encompasses antenatal and perinatal findings including antenatal ultrasound imaging of tooth buds if performed.
7. A full physical examination will be conducted at baseline, day 21, months 2, 4, and 6. With the full physical examination will be the following quantitative assessments: weight, height, head circumference and vital signs (temperature, blood pressure, heart rate and respiratory rate). A brief physical examination will be conducted at TDs 0, 1, 4, 7, 11, 14 and 15. The brief physical examination will include overall appearance (normal or abnormal and if abnormal why), skin appearance, cardiovascular, pulmonary and abdominal evaluation. With the brief physical examination will be weight and a set of vital signs (temperature, blood pressure, heart rate and respiratory rate). On dosing days vital signs will also be collected pre- and post-dosing.
8. Studies to be performed at 2 months but not at the 4-month visit. The 2-month evaluation will include pilocarpine-induced sweating but not confocal imaging (sweat duct density).
9. PK samples drawn pre-EDI200 dosing and post-end of infusion at approximately the following time points:

	Pre-Dose	**Post-Dose**							
		15 (±5) min	3 (±.5) hrs	8 (±1) hrs	18 (±2) hrs	24(±2) hrs	48 (±4) hrs	168(±8) hrs	Age 2 months (±1 wk) & 6 months (±2 wks)
D0 (dose 1)	X	X	X	X		X	X		
D14 (dose 5)	X	X	X		X		X	X	X

10. Baseline lateral jaw film only. Dental evaluation to be performed in the long-term extension study will minimize the use of dental radiographs, and allow for substitution of dental imaging obtained as part of the routine care of XLHED patients.
11. Digital analysis of non-invasive 2-Dimensional facial photographs is a technology under development jointly by the Sponsor and a private company and is being explored as a tool for monitoring change in craniofacial appearance. The algorithm assesses the subject's facial structures in the neonatal period and continues through photographs taken in the extension study.
12. Thermoregulation assessment in the neonatal period is a well-documented procedure monitoring short-term temperature and vital sign response in a closed system (incubator). At an older age in the extension study, exercise-related thermoregulation will be assessed.
13. Infections/hospitalizations as PD/efficacy endpoint will be captured through adverse events
14. No dental radiographs will be taken as part of this sibling sub-study. Subjects will be asked to provide copies of recent dental X-rays from an outside source.
15. Frontal and lateral facial photographs to be taken and baby picture (age up to 1 month) to be collected if available
16. Minimum age 5 years for pulmonary testing
17. Minimum age 4 years for eNO assessment
18. A more comprehensive dry eye assessment will be performed in children as opposed to the neonates

9.8. Changes in the Conduct of the Study or Planned Analyses

The original protocol was finalized and approved on 19 Feb 2013. Overall, there were 6 protocol amendments written and approved during the study; however, no subjects were enrolled under the Versions 1 or 2. The first protocol used to enroll subjects was Version 3, dated 24 Jun 2013. Protocol version 3.1 was UK-specific to include an optional dental ultrasound. Although changes in protocols 5.1 and 6.1 were identical to protocols 5 and 6, versions 5.1 and 6.1 were Germany-specific to account for Germany-only revisions in protocol version 4, which allowed female infants to enroll in the study. Similarly, changes in protocols 5.2 and 6.2 were identical to protocols 5 and 6, versions 5.2 and 6.2 were UK-specific to account for UK-only revisions in protocol version 3.1, which included an optional dental ultrasound.

In addition to general corrections to typographical/grammatical errors for consistency throughout protocol, substantial protocol changes that were implemented are provided in Table 4 below. The protocol and all amendments are presented in Appendix 16.1.1.

Table 4: Summary of Protocol Changes

Protocol Version	Summary of Changes
Protocol Version 3	• Added Immunogenicity to study title • Removed biopsy from Month 6 visit and PK sample from Day 15 visit • Added PK sample to baseline and Month 6 visits • Safety labs and immunogenicity sample were moved from Day 15 to Day 16 • Clarified schedule and components of brief and full physical examinations • Added provision for obtaining samples outside of specified time points • Clarified that no dental radiographs were done as part of the sibling sub-study and copies of recent dental X-rays were to be provided from an outside source • Clarification was added to Time and Events Schedule • Added clarification of dosing regimen and stratification for first subject in each cohort and subsequent cohort subjects • Added details to study drug administration procedure • Added continuous heart rate and respiratory rate monitoring during and for 24 hours following dosing study drug administration, pre- and post-dosing vital sign monitoring, and infusion site monitoring • Allowed for the use of other tools for development assessment • Removed statement allowing genetic testing to be performed at the study site if not previously performed • Added clarification of PI responsibility for assessment of lab values using both Common Terminology Criteria for Adverse Events (CTCAE) criteria and local reference ranges • Allowed for additional DSMB-requested procedures or visits and for the Sponsor or DSMB to request unscheduled visits

Protocol Version	Summary of Changes
Protocol Version 3.1[a]	• Allowed for an optional dental ultrasound
Protocol Version 4[b]	• Added female newborn inclusion criteria for Germany subjects • Removed sweat duct density and dry eye assessments from the Month 2 follow-up visit
Protocol Versions 5[c]	• Added a 3rd dosing cohort and increased dose to 30 mg/kg and other various minor changes to reflect a 3rd cohort and increased dose • Specified skin biopsy samples were not part of non-invasive evaluation of genetically related, untreated siblings • Removed sweat duct density and dry eye assessments from the Month 2 follow-up visit • Increased total study enrollment from 6-10 to 9-15 subjects
Protocol Version 6[d]	• Decreased cohort 3 study drug dosing from 30 mg/kg to 20 mg/kg and various minor changes throughout were made to reflect this change in dose

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; DSMB = Data Safety Monitoring Board; PI = principal investigator; PK = pharmacokinetic.
Note: Version 2 was issued prior to the enrollment of subjects and included only minor changes for clarification.
[a] UK only.
[b] Germany only.
[c] Although changes in protocols 5.1 and 6.1 were identical to Versions 5 and 6, versions 5.1 and 6.1 were Germany-specific to allow for female infants as revised in protocol version 4.
[d] Although changes in protocol 5.2 and 6.2 were identical to Versions 5 and 6, versions 5.2 and 6.2 were UK-specific to account for UK only revisions in protocol version 3.1.

10. STUDY PATIENTS

10.1. Disposition of Patients

A total of 10 subjects were enrolled into 3 cohorts. A summary of subject disposition is presented in Table 5.

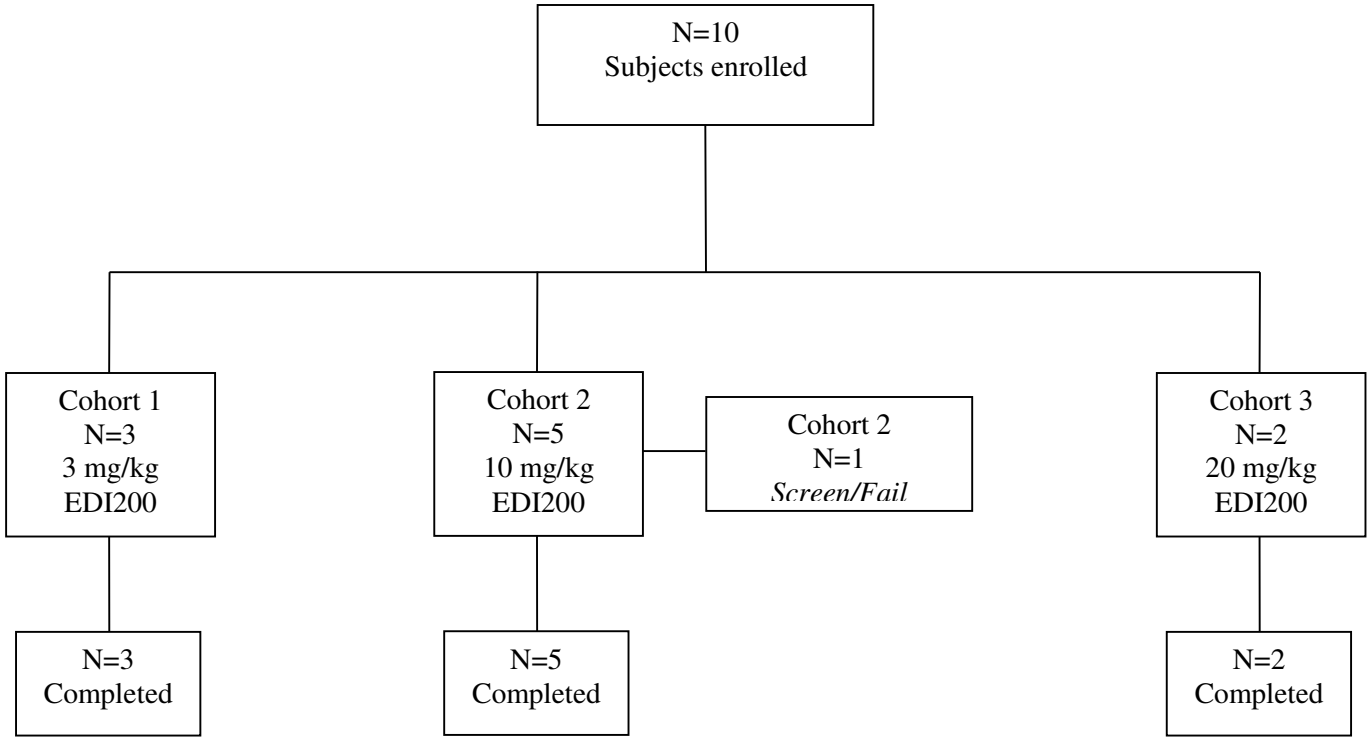
Table 5: Summary of Subject Disposition

Number of Subjects	Cohort 1 (3 mg/kg)	Cohort 2 (10 mg/kg)	Cohort 3 (20 mg/kg)	Overall N=10
Enrolled, N	3	5	2	10
Received all study drug per protocol, n (%) Yes	3 (100%)	5 (100%)	2 (100%)	10 (100%)
Completed study, n (%) Yes	3 (100%)	5 (100%)	2 (100%)	10 (100%)

Source: Table 14.1.1.

A by-subject listing of subjects and study completion is provided in Appendix Listing 16.2.1. Only subjects enrolled in the core neonate study (Protocol ECP-002) are included in this report.

Figure 1: Disposition of Patients



11. EFFICACY EVALUATION

11.1. Pharmacodynamic and Efficacy Results

11.1.1. Analysis of Efficacy

The secondary objectives of this study were to assess EDI200 pharmacodynamics (PD)/efficacy in the treatment of XLHED-affected neonates. A summary of the evaluations conducted is as follows:

- Growth and development
- Dentition
- Craniofacial development by digital photography
- Sweat duct density
- Sweat rate
- Dry eye assessments
- Thermoregulation
- Skin biopsy for molecular expression profile.

PD/efficacy evaluations were performed on all 10 subjects; however, only the clinical endpoint results of the growth and development assessments were summarized for this report. Due to the lack of efficacy of EDI200, pharmacodynamic and biomarker assessments were not summarized for this report. Data produced from the skin biopsies were archived and may be analyzed at a later date, separate from this report.

By-subject listings of the efficacy evaluation results are presented in Appendix Listings 16.2.6.2 through 16.2.6.14.

11.1.1.1. Growth and Development

Growth and development testing was performed at Baseline and Months of Life 2, 4, and 6. Testing included:

- Feeding history
- Weight, length, and head circumference for newborns
- Standard developmental milestone assessment at Baseline and validated, standard of care assessment at Months 2, 4, and 6 using tools such as the Bayley Scales of Infant Development II and the Denver Development Screening Test II Developmental assessments.

The Bayley Motor and Mental Scales of Infant Development II scores are summarized below in Table 6 and Table 7. The Bayley Scales of Infant Development III motor composite and cognitive comprehensive scores are summarized below in Table 8 and Table 9.

Table 6: Summary of Growth and Development: Bayley Scales of Infant Development II – Mental Scale

Treatment	Scheduled Visit	Raw Score						Development Index					
		n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Month 2	1	10.0		10.0	10	10	1	64.0		64.0	64	64
	Month 4	1	37.0		37.0	37	37	1	85.0		85.0	85	85
	Month 6	1	55.0		55.0	55	55	1	84.0		84.0	84	84
Cohort 2	Month 2	3	18.7	8.74	21.0	9	26	3	90.7	5.03	90.0	86	96
	Month 4	3	39.0	3.46	41.0	35	41	3	96.3	5.77	93.0	93	103
	Month 6	3	58.3	2.31	57.0	57	61	3	95.7	7.51	96.0	88	103
Overall	Month 2	4	16.5	8.35	15.5	9	26	4	84.0	13.95	88.0	64	96
	Month 4	4	38.5	3.00	39.0	35	41	4	93.5	7.37	93.0	85	103
	Month 6	4	57.5	2.52	57.0	55	61	4	92.8	8.46	92.0	84	103

Note: n represents the number of subjects contributing to summary statistics at each visit.
Source: Table 14.2.1.1; Listing 16.2.6.4.

Table 7: Summary of Growth and Development: Bayley Scales of Infant Development II – Motor Scale

Treatment	Scheduled Visit	Raw Score						Development Index					
		n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Month 2	1	13.0		13.0	13	13	1	90.0		90.0	90	90
	Month 4	1	25.0		25.0	25	25	1	89.0		89.0	89	89
	Month 6	1	38.0		38.0	38	38	1	94.0		94.0	94	94
Cohort 2	Month 2	3	14.7	5.77	18.0	8	18	3	99.3	9.81	105.0	88	105
	Month 4	3	24.0	3.00	24.0	21	27	3	89.7	4.73	88.0	86	95
	Month 6	3	34.3	2.08	35.0	32	36	3	89.0	4.58	88.0	85	94

Treatment	Scheduled Visit	Raw Score						Development Index					
		n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Overall	Month 2	4	14.3	4.79	15.5	8	18	4	97.0	9.27	97.5	88	105
	Month 4	4	24.3	2.50	24.5	21	27	4	89.5	3.87	88.5	86	95
	Month 6	4	35.3	2.50	35.5	32	38	4	90.3	4.50	91.0	85	94

Note: n represents the number of subjects contributing to summary statistics at each visit.
Source: Table 14.2.1.1; Listing 16.2.6.4.

Table 8: Summary of Growth and Development: Bayley Scales of Infant Development III – Motor Composite Score

Treatment	Scheduled Visit	Sum of Scaled Score						Composite Scores					
		n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Month 2	1	18.0		18.0	18	18	1	94.0		94.0	94	94
	Month 4	1	22.0		22.0	22	22	1	107.0		107.0	107	107
	Month 6	1	27.0		27.0	27	27	1	121.0		121.0	121	121
Cohort 2	Month 2	1	17.0		17.0	17	17	1	91.0		91.0	91	91
	Month 4	1	19.0		19.0	19	19	1	97.0		97.0	97	97
	Month 6	1	20.0		20.0	20	20	1	100.0		100.0	100	100
Cohort 3	Month 2	1	22.0		22.0	22	22	1	107.0		107.0	107	107
	Month 4	1	27.0		27.0	27	27	1	121.0		121.0	121	121
	Month 6	1	15.0		15.0	15	15	1	85.0		85.0	85	85
Overall	Month 2	3	19.0	2.65	18.0	17	22	3	97.3	8.50	94.0	91	107
	Month 4	3	22.7	4.04	22.0	19	27	3	108.3	12.06	107.0	97	121
	Month 6	3	20.7	6.03	20.0	15	27	3	102.0	18.08	100.0	85	121

Note: n represents the number of subjects contributing to summary statistics at each visit.
Source: Table 14.2.1.2; Listing 16.2.6.4.

Table 9: Summary of Growth and Development: Bayley Scales of Infant Development III – Cognitive Comprehensive Score

Treatment	Scheduled Visit	Sum of Scaled Score						Composite Scores					
		n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Month 2	1	7.0		7.0	7	7	1	85.0		85.0	85	85
	Month 4	1	12.0		12.0	12	12	1	110.0		110.0	110	110
	Month 6	1	11.0		11.0	11	11	1	105.0		105.0	105	105
Cohort 2	Month 2	1	12.0		12.0	12	12	1	110.0		110.0	110	110
	Month 4	1	11.0		11.0	11	11	1	105.0		105.0	105	105
	Month 6	1	10.0		10.0	10	10	1	100.0		100.0	100	100
Cohort 3	Month 2	1	11.0		11.0	11	11	1	105.0		105.0	105	105
	Month 4	1	13.0		13.0	13	13	1	115.0		115.0	115	115
	Month 6	1	10.0		10.0	10	10	1	100.0		100.0	100	100
Overall	Month 2	3	10.0	2.65	11.0	7	12	3	100.0	13.23	105.0	85	110
	Month 4	3	12.0	1.00	12.0	11	13	3	110.0	5.00	110.0	105	115
	Month 6	3	10.3	0.58	10.0	10	11	3	101.7	2.89	100.0	100	105

Note: n represents the number of subjects contributing to summary statistics at each visit.
Source: Table 14.2.1.2; Listing 16.2.6.4.

12. SAFETY EVALUATION

12.1. Extent of Exposure

All subjects in the study population (10/10, 100%) completed administration of EDI200 dosing. Cohorts 1 (n=3), 2 (n=5), and 3 (n=2) received 3 mg/kg, 10 mg/kg, and 20 mg/kg doses of EDI200, administered intravenously, on Days 0, 4, 7, 11, and 14, respectively.

A population pharmacokinetic analysis was performed to estimate PK parameters from serial blood draws for 10 neonatal subjects. A three-compartment weight-normalized linear model with elimination from the central compartment, based on the modeling used in previous studies of adults, was evaluated. The value for clearance was similar to that determined in adults. Estimated PK parameters are presented in the following table.

Table 10: Pharmacokinetic Parameters from the Optimal Weight-normalized Model in Adults

Parameter	Typical Value
Clearance (L/day)	21.4507 • (WT / 86.8)
Volume of the central compartment (L)	7.87249 • (WT / 86.8)
Distribution clearance (L/day)	92.4160 • (WT / 86.8)
Volume of the peripheral compartment (L)	19.7833 • (WT / 86.8)
Slow distribution clearance (L/day)	13.9319 • (WT / 86.8)
Volume of the deep peripheral compartment (L)	76.1963 • (WT / 86.8)

Abbreviations: WT = weight.

A by-subject listing of treatment exposure is presented in Appendix Listing 16.2.5, and the final PK report is provided in Appendix 16.6.

12.2. Adverse Events

12.2.1. Brief Summary of Adverse Events

A summary of adverse events (AEs) considered treatment-emergent that occurred between dosing and the end of the designated follow-up period (6 months) is provided in Table 11 below. Overall, all 10 subjects (100%) experienced a total of 166 treatment-emergent adverse events (TEAEs) during the study. One TEAE (1/166, 0.6%) was considered to be probably related to study drug, and 41 TEAEs (41/166, 24.7%) were considered to be possibly related to study drug.

Cumulatively, 154 TEAEs (154/166, 92.8%) were of mild intensity, 4 (4/166, 2.4%) were moderate, and 6 (6/166, 3.6%) were severe. Of the 166 TEAEs, 6 (6/166, 3.6%) were considered a treatment-emergent serious adverse event (TESAE) and were experienced in 5 subjects (5/10, 50.0%). None of the events led to discontinuation of study drug or discontinuation of participation in the study.

12.2.2. Display of Adverse Events

The TEAEs reported are summarized in Table 12 below by System Organ Class (SOC). A summary of the overall TEAEs on a preferred term (PT) level is presented in Appendix Listing 16.2.7.

Table 11: Overall Summary of Treatment-Emergent Adverse Events

	Cohort 1 (3 mg/kg dose) N=3		Cohort 2 (10 mg/kg dose) N=5		Cohort 3 (20 mg/kg dose) N=2		Overall N=10	
	Subjects (%) [1]	No. of Events [2]	No. of Subjects (%) [1]	No. of Events [2]	No. of Subjects (%) [1]	No. of Events [2]	No. of Subjects (%) [1]	No. of Events [2]
Subjects with at least one TEAE	3 (100%)	49	5 (100%)	70	2 (100%)	47	10 (100%)	166
Relationship to Study Treatment, n (%)								
Probably	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1
Possibly	1 (33.3%)	13	2 (40.0%)	27	1 (50.0%)	1	4 (40.0%)	41
Unlikely	2 (66.7%)	30	2 (40.0%)	19	1 (50.0%)	27	5 (50.0%)	76
Not Related	0 (0.0%)	6	0 (0.0%)	23	0 (0.0%)	19	0 (0.0%)	48
Intensity								
Mild	1 (33.3%)	46	1 (20.0%)	63	0 (0.0%)	45	2 (20.0%)	154
Moderate	1 (33.3%)	1	2 (40.0%)	2	1 (50.0%)	1	4 (40.0%)	4
Severe	1 (33.3%)	2	2 (40.0%)	3	1 (50.0%)	1	4 (40.0%)	6
Life Threatening	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0
Subjects with at least one TESAE, n (%)	1 (33.3%)	1	3 (60.0%)	4	1 (50.0%)	1	5 (50.0%)	6
TEAEs leading to study treatment discontinuation, n (%)	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0

TEAE=Treatment-emergent Adverse Event; TESAE=Treatment-emergent Serious Adverse Event; Treatment-emergent refers to events occurring on or after the day of study drug administration;

[1] At each level of summation (relationship, intensity grade), subjects reporting more than one TEAE were counted only once using the strongest relationship to study medication, maximum intensity, and maximum toxicity grade.

[2] Number of events includes all occurrences of events.

Source: Table 14.3.1.1; Listing 16.2.7.

Table 12: Summary of Treatment-emergent Adverse Events by System Organ Class and Preferred Term

System Organ Class	Cohort 1 (3 mg/kg dose) N=3		Cohort 2 (10 mg/kg dose) N=5		Cohort 3 (20 mg/kg dose) N=2		Overall N=10	
	No. of Subjects (%) [1]	No. of Events [2]	No. of Subjects (%) [1]	No. of Events [2]	No. of Subjects (%) [1]	No. of Events [2]	No. of Subjects (%) [1]	No. of Events [2]
All Body Systems	3 (100%)	49	5 (100%)	70	2 (100%)	47	10 (100%)	166
Blood and Lymphatic System Disorders	2 (66.7%)	6	4 (80.0%)	7	1 (50.0%)	3	7 (70.0%)	16
Congenital, Familial, and Genetic Disorders	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1
Gastrointestinal Disorders	0 (0.0%)	0	1 (20.0%)	1	2 (100%)	2	3 (30.0%)	3
General Disorders and Administration Site Conditions	0 (0.0%)	0	1 (20.0%)	1	1 (50.0%)	1	2 (20.0%)	2
Infections and Infestations	2 (66.7%)	2	4 (80.0%)	7	1 (50.0%)	1	7 (70.0%)	10
Injury, Poisoning, and Procedural Complications	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1
Investigations	3 (100%)	34	5 (100%)	45	2 (100%)	34	10 (100%)	113
Metabolism and Nutrition Disorders	1 (33.3%)	3	3 (60.0%)	4	0 (0.0%)	0	4 (40.0%)	7
Pregnancy, Puerperium, and Perinatal Conditions	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	2	1 (10.0%)	2
Psychiatric Disorders	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1
Renal and Urinary Disorders	1 (33.3%)	2	0 (0.0%)	0	1 (50.0%)	1	2 (20.0%)	3
Respiratory, Thoracic, and Mediastinal Disorders	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1

System Organ Class	Cohort 1 (3 mg/kg dose) N=3		Cohort 2 (10 mg/kg dose) N=5		Cohort 3 (20 mg/kg dose) N=2		Overall N=10	
	No. of Subjects (%) [1]	No. of Events [2]	No. of Subjects (%) [1]	No. of Events [2]	No. of Subjects (%) [1]	No. of Events [2]	No. of Subjects (%) [1]	No. of Events [2]
Skin and Subcutaneous Tissue Disorders	1 (33.3%)	1	1 (20.0%)	4	1 (50.0%)	1	3 (30.0%)	6

Note: AEs summarized potentially include both serious and non-serious AEs.
AEs were considered treatment-emergent if they occurred on the same day of study drug administration or after.
Percentages are based on the total number of subjects in each treatment group (N).
Any subject with multiple events in one System Organ Class (SOC) was counted only once for that SOC, using the event with the highest toxicity grading.
Any subject with multiple events in one Preferred Term (PT) was counted only once for that PT, using the event with the highest toxicity grading.
Source: Table 14.3.1.4; Listing 16.2.7.

12.2.3. Analysis of Adverse Events

EDI200 was generally well tolerated, and all subjects completed the study per protocol. Overall, 166 TEAEs were reported in 10 subjects. One event was considered probably related to study treatment, and 41 events were considered possibly related to study treatment. None of the TEAEs were considered to be life threatening or led to discontinuation in the study. There were no deaths related to an AE.

In cohort 1 (3 mg/kg/dose), the 3 subjects (3/3, 100%) experienced a combined 49 TEAEs: 46 (93.9%) events were mild in intensity, 1 (2.0%) event was moderate, and 2 (4.1%) were severe. None of the TEAEs were considered definitely or probably related to study treatment, while 13 were considered possibly related to study drug. Both events considered severe in intensity were experienced in one subject. Subject 3063-001 experienced hyponatremia on Day 16, which resolved on Day 23. The AE resolved spontaneously without treatment, and the event was graded as severe in intensity and possibly related to study medication. In addition, the subject also experienced a respiratory syncytial virus (RSV) infection on Day 146. The event of RSV infection occurred 131 days after the last dose of study medication, and the event was determined to be a serious adverse event (SAE) due to hospitalization or prolonged hospitalization. The event was graded as severe in intensity but was not considered to be related to study medication.

In cohort 2 (10 mg/kg/dose), the 5 subjects (5/5, 100%) experienced a combined 70 TEAEs: 63 (90.0%) events were mild in intensity, 2 (2.9%) were moderate, 3 (4.3%) were severe, and 2 (2.9%) were reported without a Common Terminology Criteria for Adverse Events (CTCAE) grade. One event, small edema at injection site in Subject 3063-004, was considered probably related to study medication, but it was graded as mild in intensity. Two TEAEs were not reported with a CTCAE grade by the investigative site, both for Subject 3063-002 in cohort 2; however, per Investigator Assessment, both TEAEs were mild in intensity. A total of 4 TESAEs were experienced in 3 subjects, including pyelonephritis (moderate in intensity), febrile upper respiratory infection (severe in intensity), bronchiolitis (severe in intensity), and bronchopneumonia (severe in intensity).

For the 2 subjects in cohort 3 (20 mg/kg/dose), a total of 47 TEAEs were experienced: 45 (95.7%) events were mild in intensity, 1 (2.1%) was moderate, and 1 (2.1%) was severe. One event (1/47, 2.1%) was considered possibly related to study medication, while the remaining 46 TEAEs were considered either unlikely (27/47, 57.4%) or not related (19/47, 40.4%) to study medication. Subject 3064-002 experienced 1 TESAE of lower respiratory tract infection. The event was severe in intensity but was not considered to be related to study medication.

12.2.4. Listing of Adverse Events by Patient

By-subject listings of adverse events are presented in Appendix Listing 16.2.7. The listings are sorted by cohort group and subject number and include System Organ Class, preferred term, start date/time, end date/time, intensity, toxicity, relationship, action taken, outcome, whether the subject withdrew, and whether the event was treatment-emergent.

12.3. Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1. Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

There were no deaths or other significant adverse events in this study. By-subject listings of SAEs are included in Appendix Listing 16.2.7.

12.3.1.1. Other Serious Adverse Events

Overall, 5 subjects (50.0%) experienced a total of 6 TESAEs. A summary of TESAEs that occurred between dosing and the end of follow-up is provided in Table 13.

Table 13: Summary of Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term

System Organ Class Preferred Term	Cohort 1 N=3		Cohort 2 N=5		Cohort 3 N=2		Overall N=10	
	No. of Subjects (%)	No. of Events	No. of Subjects (%)	No. of Events	No. of Subjects (%)	No. of Events	No. of Subjects (%)	No. of Events
All body systems	1 (33.3%)	1	3 (60.0%)	4	1 (50.0%)	1	5 (50.0%)	6
Infections and Infestations								
Bronchiolitis	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1
Bronchopneumonia	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1
Lower respiratory tract infection	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1
Pyelonephritis	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1
Respiratory syncytial virus infection	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1
Upper respiratory tract infection	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1

Treatment-emergent SAEs were considered treatment-emergent if they occurred after administration of study drug.
Percentages were based on the total number of subjects in each treatment group (N).
Any subject with multiple events in one System Organ Class (SOC) was counted only once for that SOC.
Any subject with multiple events in one Preferred Term (PT) was counted only once for that PT.
Source: Table 14.3.1.6; Listing 16.2.7.

12.3.2. Narratives of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events

Narratives for the subjects who experienced an SAE are presented in Appendix 16.4.

12.3.3. Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Overall, all 6 TESAEs experienced in the study were considered to be either not related (n=3) or unlikely related (n=3) to study medication. Furthermore, all TESAEs were treated successfully, and no change was required with regards to study medication.

12.4. Clinical Laboratory Evaluation

12.4.1. Listing of Individual Laboratory Measurements by Patient and Each Abnormal Laboratory Value

Serum chemistry, hematology, and urinalysis were performed at Baseline, Days 1, 16, and 21, and follow-up visits at 2, 4, and 6 Months of Life.

By-subject details of all safety laboratory tests performed during this study can be found in Appendix Listing 16.2: biochemistry (Listing 16.2.8.1), hematology (Listing 16.2.8.2), and urinalysis results (Listing 16.2.8.3). Laboratory results tables summarizing the change of values between Baseline and various post-dose time points (Day 1, 16, 21, Month 2, and Month 6) are located by cohort treatment group for chemistry (Table 14.3.4.1) and hematology (Table 14.3.4.2).

12.4.2. Evaluation of Each Laboratory Parameter

12.4.2.1. Laboratory Values Over Time

Overall, there were no clinically meaningful differences or mean changes from Baseline in the laboratory values among cohort groups.

12.4.2.2. Individual Subject Changes

Individual clinical laboratory assessments are presented in Appendix 16.2 with by-subject listings of biochemistry (Listing 16.2.8.1), hematology (Listing 16.2.8.2), and urinalysis results (Listing 16.2.8.3). Any results outside of the reference range are indicated as being high or low in the listing (Listing 16.2.8.4).

While there were shifts for some laboratory parameters from the normal range to outside the normal range in some subjects, there was no consistent pattern in shifts in laboratory parameter values by treatment groups. Furthermore, no individual laboratory value was considered an AE for any subject. More details can be found in the by-subject listings mentioned above.

12.5. Immunogenicity Testing

All 10 subjects underwent blood sampling for immunogenicity testing for the appearance or absence of anti-drug antibodies (ADA) at Baseline, Day 16, Month 2, and Month 6. No anti-EDI200 antibodies were detected in any subject.

Individual ADA results are presented in Appendix 16.7.

12.6. Vital Signs, Physical Findings, and Other Observations Related to Safety

12.6.1. Vital Signs

Blood pressure, heart rate, respiratory rate, and temperature were measured continuously at the following: at Baseline (day-of-life 2 to 14), pre-dose within 1 hour of initiation of dose infusion, post-dosing at 15 minutes, 1 hour, and 4 hours, then every 4 hours up to 24 hours after the end of infusion on Treatment Days (TD) 0, 4, 7, 11 and 14, as well as TD 15 and 21, and at follow-up visits at 2, 4, and 6 Months of Life.

There were no clinically meaningful differences or changes from baseline. By-subject listings of vital signs are presented in Appendix Listing 16.2.9 and summarized in Table 14.3.4.5.

12.6.2. Physical Examination

Full physical examinations, including weight, height, and head circumference, were conducted at Baseline, Day 21, Months of Life 2, 4, and 6. A brief physical examination was conducted at TDs 0, 1, 4, 7, 11, 14, and 15. The brief physical examination was to include overall appearance (normal or abnormal and, if abnormal, why), skin appearance, cardiovascular, pulmonary, and abdominal evaluation. Weight was also measured with brief physical examinations.

Any abnormalities were captured as part of medical history or AEs. A finding was reported as an AE if it was a change from Baseline (Screening) and was considered by the PI to be clinically significant. By-subject listings are presented in Appendix Listing 16.2.11.

12.7. Safety Conclusions

In this study, the DSMB met after the dosing period for each enrolled subject, and each time the DSMB recommended dosing of the subsequent subject. The DSMB also met in April 2014 to review all of the data, including pharmacokinetics, from the first cohort and approved the progression to the second cohort (10 mg/kg). In addition, the DSMB met in February 2015 to discuss the proposed dose of 30 mg/kg for the third study cohort, a 3-fold increase from the prior cohort.

Although the DSMB was reassured by the lack of safety concerns at that time, it recommended that the dose for the third cohort be increased to 20 mg/kg, rather than 30 mg/kg. The DSMB also requested the PK data be provided to the DSMB on a subject-by-subject basis as soon as possible, although not necessarily at the time of the initial safety review, to approve dosing of the next subject.

The DSMB believed the more conservative approach was justified for the following reasons:

1. Newborn infants are a vulnerable population and it can be difficult to predict drug metabolism in neonates.
2. The number of infants assessed to date was still quite low, and the site-based PK issues mentioned above further limited the assessment of drug exposure. Together these factors suggested a need to be conservative in dose escalation.
3. The suggested doubling of the dose to 20mg/kg represented an increase in dose with a reasonable potential to be efficacious, based on the animal data.

In this first-in-neonate, open-label Phase 2 dose-escalation study, 10 subjects (100%) experienced a total of 166 TEAEs during the study, and there were 6 TESAEs. EDI200 was administered in doses of 3 mg/kg (n=3), 10 mg/kg (n=5), and 20 mg/kg (n=2). Five subjects (50%) experienced a total of 6 TESAEs during the completed neonate intervention study (ECP-002). The TESAEs were bronchiolitis (n=1), bronchopneumonia (n=1), lower respiratory tract infection (n=1), pyelonephritis (n=1), RSV infection (n=1), and upper respiratory tract infection (n=1). All TESAEs were treated successfully, considered unlikely related or not related to study medication, and required no change with regards to study medication. There were no deaths in the study, and none of the TEAEs led to study discontinuation. None of the abnormalities reported in clinical laboratory parameters, physical findings, and vital signs were determined to be adverse events.

13. DISCUSSION AND OVERALL CONCLUSIONS

13.1. Conclusions

This trial was a first-in-neonate, open-label, multicenter Phase 2 dose-escalation study of EDI200 administered to XLHED-affected infants. Its design incorporated the experience gained from the previously complete adult study. The study successfully met its goals of enrolling 3 cohorts and completing the planned course of 5 IV doses in every one of the 10 subjects. DSMB involvement and review of the Phase 2 study results contributed to the determination of final parameters for study treatment doses and monitoring in this study.

The primary objectives of demonstrating safety and determining immunogenicity and PK were met. Immunogenicity was measured by the presence or absence of ADA in the serum. All subjects enrolled into the 3 cohorts and dosed with EDI200 had negative ADA results. Therefore, no clinical events or significant changes in PK were assessed as affected by the presence of anti-EDI200 antibodies. The PK analysis showed that the value for clearance in all of the weight-normalized models was similar to the value determined in adults.

The secondary objective of this study was to assess the PD/efficacy of EDI200 in the treatment of XLHED-affected neonates. There were no clinically significant differences between treatment groups in growth and development assessments or other key measures of disease response available at the time of this report. Pharmacodynamic assessments appeared to indicate that, following 2, 4, and 6 months after completion of EDI200 treatment, there were minimal to no improvements in the thermoregulation and growth and development (Bayley Scales of Infant Development II or III) assessments. These results may reflect the small sample size of the study.

Overall, EDI200 was generally well tolerated and the development of ADA was not seen in any of the 10 subjects. No significant actions were taken with EDI200 for safety reasons. No safety risks of EDI200 were identified that would have required major changes to the design of the completed clinical study, to the doses that were administered, or to the clinical development plan for EDI200.

14. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

Not Applicable.

15. REFERENCE LIST

Cluzeau C, Hadj-Rabia S, Bal E, Clauss F, Munnich A, Bodemer C, Headon D, Smahi A. (2012) The EDAR370A allele attenuates the severity of hypohidrotic ectodermal dysplasia caused by EDA gene mutation. *Br J Dermatol* 166:678-81.

16. APPENDICES

16.1.1. Protocol and Protocol Amendments

16.1.2. Sample Case Report Forms (Unique pages only)

16.2. Data Listings

16.3. CRFs for Subjects Who Experienced a Serious Adverse Event

16.4. DSMB Charter and Meeting Minutes

16.5. Narratives for Subjects Who Experienced a Serious Adverse Event

16.6. Pharmacokinetic Report

16.7. Individual Subject Immunogenicity Listing

Appendix 16.1.1- Protocol and Protocol Amendments

Note: Versions 1 and 2 were issued prior to the enrollment of subjects and included only minor changes for clarification.

[a] Although changes in protocols 5.1 and 6.1 were identical to Versions 5 and 6, versions 5.1 and 6.1 were Germany-specific to allow for female infants as revised in protocol version 4.

[b] Although changes in protocol 5.2 and 6.2 were identical to Versions 5 and 6, versions 5.2 and 6.2 were UK-specific to account for UK only revisions in protocol version 3.1.

Protocol Version 3
24 Jun 2013

Clinical Protocol

A Phase 2 open-label, dose-escalation study to evaluate the safety, pharmacokinetics, immunogenicity and pharmacodynamics/efficacy of EDI200, an EDA-A1 replacement protein, administered to male infants with X-Linked Hypohidrotic Ectodermal Dysplasia (XLHED)

Protocol: ECP-002

Investigational Product: EDI200

Sponsor:

Edimer Pharmaceuticals, Inc.
55 Cambridge Parkway
Suite 102W
Cambridge MA 02142

IND Number: 109262
EudraCT Number: 2012-003561-17

Issue Date: 24JUN2013
Version: 3

TABLE OF CONTENTS

PROTOCOL AMENDMENTS

Previous Versions
19FEB2013, original
02APR2013, version 2*
*Version 2 was issued prior to the enrollment of subjects and included only minor changes for clarification

Amendment #/Date	Applicable Section	Original Text	New/Revised Text/Description	Rationale
3 12JUN2013	Cover Page, Synopsis	A Phase 2 open-label, dose-escalation study to evaluate the safety, pharmacokinetics and pharmacodynamics/efficacy of EDI200, an EDA-A1 replacement protein, administered to male infants with X-Linked Hypohidrotic Ectodermal Dysplasia (XLHED)	A Phase 2 open-label, dose-escalation study to evaluate the safety, pharmacokinetics, immunogenicity and pharmacodynamics/efficacy of EDI200, an EDA-A1 replacement protein, administered to male infants with X-Linked Hypohidrotic Ectodermal Dysplasia (XLHED)	Immunogenicity added to study title
3 12JUN2013	Executive Summary	See 02APR2013 protocol version 2	Several minor changes made to Executive Summary	Clarification
3 12JUN2013	Time and Events Schedule	Change made to biopsy and PK sample schedule	Biopsy removed from Month 6 visit, PK sample removed from Day 15 visit	Correction and clarification
3 12JUN2013	Time and Events Schedule	Change made to PK sample schedule	PK sample added to baseline and month 6	Modification of PK sample schedule (similar minor changes made throughout protocol)
3 12JUN2013	Time and Events Schedule	Change made to safety labs and immunogenicity sample schedule	Safety labs and immunogenicity sample moved from day 15 to day 16	Modification of safety labs and immunogenicity sample schedule (similar minor changes made throughout protocol)
3 12JUN2013	Time and Events Schedule	A full physical exam will be conducted at baseline, treatment days 7 and 14 and at the months 2, 4 and 6 follow-up visits. The full physical exam will include weight, height, head circumference and vital signs. A brief physical exam will be conducted at treatment days 0, 1, 4, 11, 15 and 21. The brief	A full physical examination will be conducted at baseline, day 21, months 2, 4, and 6. With the full physical examination will be the following quantitative assessments; weight, height, head circumference and vital signs (temperature, blood pressure, heart rate and respiratory rate). A brief physical examination will be	Clarification on components of brief and full physical exam

		physical exam will include vital signs. On dosing days vital signs will also be collected every 4 hours following the end of the infusion for 24 hours.	conducted at treatment days 0, 1, 4, 7, 11, 14 and 15. The brief physical examination will include overall appearance (normal or abnormal and if abnormal why), skin appearance, cardiovascular, pulmonary and abdominal evaluation. With the brief physical examination will be weight and a set of vital signs (temperature, blood pressure, heart rate and respiratory rate). On dosing days vital signs will also be collected pre- and post dosing as described in section 3.3.8.	
3 12JUN2013	Time and Events Schedule, 4.5.2	New text added	Time windows added for acceptable sampling	Provision for obtaining samples outside of specified time points
3 12JUN2013	Time and Events Schedule	Subjects may provide dental X-rays from an outside source. No dental radiographs will be obtained at the study site.	No dental radiographs will be taken as part of this sibling sub-study. Subjects will be asked to provide copies of recent dental X-rays from an outside source.	Clarification that no dental radiographs are done as part of the sibling sub-study (similar minor changes made throughout protocol)
3 12JUN2013	Time and Events Schedule	See 02APR2013, protocol version 2	Several minor changes made to Time and Events Schedule	Clarification
3 12JUN2013	1.1	See 02APR2013, protocol version 2	Several minor changes made	Clarification
3 12JUN2013	3	See 02APR2013, protocol version 2	Several minor changes made	Clarification
3 12JUN2013	3.1.5	The schedule of events for the In-Clinical portion of the study is presented in the Time and Events Table. In each cohort the first subject enrolled will complete dosing of study medication, and if no significant AEs are observed then the remaining cohort subjects may begin dosing one week	The subject will be admitted to the study site during the entire dosing period. The schedule of events for this portion of the study is presented in the Time and Events Table. In each cohort, the first subject enrolled will complete the 15-day dosing period and undergo monitoring for an additional	Clarification of dosing stratification

		later. Subjects will have vital sign monitoring during and for 24 hours following each dose of study drug. The Medical Monitor and study PI will be responsible for evaluation of all AE and safety laboratory results.	week at the study site. The site and Sponsor Medical Monitors will then review all AE and safety laboratory data. In the absence of any clinically significant AE's the remaining cohort subjects may begin dosing. It is anticipated that the timeframe from last dose of the first cohort subject through AE review will be approximately 2 weeks.	
3 12JUN2013	3.3.4, 3.3.6, 3.3.7	FDA	National Competent Authorities	Term FDA replaced with National Competent Authorities
3 12JUN2013	3.3.8	EDI200 will be thawed to room temperature on the day of dose administration, pooled in syringe(s) and infused via a syringe pump infusion system. The study drug shall be infused routinely over a period of 2 hours, but not to exceed 5 ml/kg/hr or 500 mg EDI200/hr.	EDI200 will be thawed to room temperature on the day of dosing, pooled in syringe(s) and administered via a syringe pump infusion system. The study drug shall be administered by slow IV infusion over at least 30 min, not to exceed 5 ml/kg/hour or 8.5 mg/min EDI200, in order to minimize the risk of infusion-related AE (refer to Investigational Brochure, Section 6.2). For more information on the preparation of EDI200 see the Pharmacy/Investigator Manual.	Clarification of infusion procedure
3 12JUN2013	3.3.8	New text added	During study drug administration and for 24 hrs following infusion the subject will have continuous heart rate and respiratory rate monitoring. A full set of vital signs including temperature, blood pressure, heart rate and respiratory rate will be documented on the following schedule: • Pre dosing - a single set of vital signs within 1 hour of initiating dose infusion • Post dosing:	Clarification of continuous monitoring (similar minor changes made throughout protocol)

			○ 15 min after end of infusion, ○ 1 hr and 4 hrs after end of infusion, ○ then q4 hrs up to 24 hrs after end of infusion If the unit in which the subject is receiving study drug requires additional monitoring, then that data will be added to the subject's record.	
3 12JUN2013	3.3.8	New text added	The intravenous site will be assessed for patency and signs of local irritation prior to the start of the infusion, every 30 minutes during infusion, and at the end of study drug infusion.	Clarification of infusion site monitoring
3 12JUN2013	4.2.1	The initial physical examination will include assessment of standard developmental milestones, and will be augmented at Months 2, 4 and 6 by the Bayley Scales of Infant Development II (BSID-II), a well-validated assessment tool for use at 1-42 months of age (Black and Matula, 2000).	The initial physical examination will include assessment of standard developmental milestones, and will be augmented at Months 2, 4 and 6 by a validated, standard of care infant assessment tool. Examples of such tools include but are not limited to the Bayley Scales of Infant Development II (BSID-II) and III (BSDI-III) and the Denver Development Screening Test II (DDST II) (Black and Matula, 2000). Whichever tool is selected should be designed for ages down to 2 months of life and should be used for all follow-up visits.	Provision for the use of other tools of development assessment
3 12JUN2013	4.3	To meet inclusion criteria for study drug administration, families of potential study subjects will be asked if their male newborn has been tested for EDA mutations that confirm the XLHED diagnosis, either prenatally or postnatally. If genetic testing has been done,	To meet inclusion criteria for EDI200 administration, potential study subjects are required to have their XLHED diagnosis confirmed by genetic testing of the EDA gene and these test results relayed to the study site. EDA genetic testing itself is outside of the scope of this protocol. If requested, the	Clarification of genetic testing done during screening

		verbal consent from the family will be obtained to provide documentation of test results to the study site via a secure and confidential method including an option for electronic transmission. If not, the study site will provide a genotyping kit with an informed consent form directly to the family (no provision for fetal or amniotic fluid testing as part of this protocol). All genotyping costs will be covered by the study. It will be the responsibility of the family to have cord blood or a neonatal blood sample drawn and sent to the recommended genotyping laboratory.	families of prospective subjects in need of EDA genotyping will be referred to resources available to facilitate this testing. Consent from the family (written or verbal) will be obtained as part of the screening process to provide the study site with documentation of genetic testing results via a secure and confidential method including an option for electronic transmission.	
3 12JUN2013	4.5.1	New text added	It will be the Principal Investigator's responsibility to assess laboratory parameters against local reference ranges and to assess the clinical significance of any out of range values.	Clarification on assessment of lab values using both CTCAE criteria and local reference ranges
3 12JUN2013	4.6.2	The PI will report all SAEs to the Sponsor in a timely fashion, usually within 24 hours of awareness, by completing and faxing the SAE Report Form to CTI Safety as per directions described in the Study Reference Manual.	The PI will report all SAEs to the Sponsor in a timely fashion, within 24 hours of awareness, by completing and faxing the SAE Report Form to CTI Safety as per directions described in the Study Reference Manual.	Word "usually" deleted as reporting requirements are within 24 hours
3 12JUN2013	4.8	Unscheduled DSMB reviews will take place as outlined in Section 3.3.4-3.3.7 for single or accumulated adverse events.	Unscheduled DSMB reviews will take place as outlined in Section 3.3.4-3.3.7 for single or accumulated adverse events. Additional safety-related evaluations of one or more subjects may be requested by the DSMB based on findings through the 6 month, end-of-study visit.	Provision to allow for additional DSMB-requested procedures or visits
3	5.5	New text added	The Sponsor or DSMB may	Provision to

12JUN2013			request unscheduled visits either during the subject's participation in the Study or after his completion. The unscheduled visits may include additional safety-related evaluations (including blood sampling) based on findings through the 6-month, end-of-study visit.	allow for unscheduled visits

EXECUTIVE SUMMARY

X-linked hypohidrotic ectodermal dysplasia (XLHED) is a disorder of ectoderm development in which sweat and secretory gland hypoplasia predisposes affected infants to serious and potentially life-threatening hyperthermia and pneumonia (Clarke et al., 1987). Those XLHED patients who survive infancy face a host of ectoderm-related clinical conditions including failure to thrive, oligodontia and misshapen teeth, mid-face hypoplasia, eczema, chronic dry eyes, asthma, respiratory infections, sinusitis and chronic nosebleeds. XLHED is caused by inherited defects in the ectodysplasin gene (EDA, www.ncbi.nlm.nih.gov/omim) resulting in a deficiency of the ectoderm signaling protein EDA-A1. As is the general case with X-linked disorders, hemizygous XLHED males are more consistently and severely affected, while heterozygous XLHED females have a more variable phenotype.

In normal development, EDA-A1 acts as an ectoderm signaling molecule that binds specifically to the EDA-A1 receptor (EDAR) triggering initiation and maturation of ectoderm appendages into sweat and secretory glands, tooth buds and hair follicles. In the case of XLHED, EDA-A1 deficiency results in the absence or functional hypoplasia of the ectoderm appendages. There are no therapies currently available for XLHED that prevent or correct the underlying ectodermal abnormalities.

EDI200 is a fully humanized EDA-A1 replacement molecule under development as a novel therapeutic for XLHED. EDI200 comprises the human IgG1 Fc domain linked to the human EDA-A1 receptor-binding domain. In the course of normal ectodermal signaling, EDA-A1 monomers associate as trimers and higher order multimers that are required for activation of the EDA-A1 receptor (EDAR). The N-terminal Fc receptor portion of the EDI200 molecule serves to stabilize the intermolecular EDA-A1 associations required for EDAR binding, and to provide a potential mechanism for transplacental delivery (Miller, 2003).

On-target EDI200 activation of the EDA-A1/EDAR signaling pathway *in vivo* is evidenced by the remarkable phenotypic response in preclinical models. In XLHED-affected animals, EDI200 correction of EDA-A1 deficiency prenatally (mice) or postnatally (newborn mice and dogs) resulted in a significant and sustained improvement in the health of the treated animals (Gaide and Schneider, 2003; Casal et al., 2007; Mauldin et al., 2009). Postnatal studies in both mice and dogs demonstrated a consistent and restricted window of efficacy (Gaide and Schneider, 2003; Edimer Study NCD-11-200-005). These results support the clinical development of EDI200 as a therapeutic to be administered to XLHED-affected patients in the neonatal period or earlier.

This Phase 2 first-in-neonate study will enroll treatment-naïve, XLHED-affected male newborns for EDI200 administration initiated within the first two weeks of life. All subjects will meet entry criteria including documentation of an EDA mutation associated

with XLHED. Following Baseline evaluations, EDI200 dosing will be initiated between day-of-life (DOL) 2 and 14, with each study subject receiving 2 doses/week for a total of 5 doses. This dosing regimen mirrors that used to enhance efficacy in the dog XLHED model, considered to be most relevant to the clinical study design. Comprehensive safety, pharmacokinetic (PK), immunogenicity and pharmacodynamic (PD)/efficacy evaluations of all neonate study subjects will initiate at study enrollment and continue throughout the dosing and follow-up period (to age 6 months).

The study will enroll 6-10 subjects in two cohorts, with a minimum of 3 subjects per cohort. Given the challenge of identifying families where the potential study subject is yet to be born, it is expected that cohort size and time for recruitment will be variable. We anticipate enrolling subjects over a 12-18 month period. Cohort 1 study subjects will each be administered EDI200 IV at 3 mg/kg/dose x 5 doses, equivalent to 0.015 x the neonate no observed adverse effect level (NOAEL) of 200 mg/kg/dose (factor of 1:66) and well below the maximum safe starting dose in initial clinical trials as suggested by FDA guidance. This dose was associated with partial efficacy in the canine XLHED model considered most relevant to the clinical study, and was well tolerated by XLHED adults in the Phase 1 safety study (NCT01564225, www.clinicaltrials.gov)

All safety laboratory studies will be done at the individual study sites and available to the Data Safety Monitoring Board (DSMB) in real time. Following dosing of all subjects in neonate cohort 1, the DSMB will review the cohort 1 safety and PK data. If no new safety issues are identified then cohort 2 subjects will be enrolled and dosed at a ½ log increase to 10 mg/kg/dose IV, equivalent to 0.05 x the neonate NOAEL of 200 mg/kg/dose (factor of 1:20). This dose was associated with enhanced efficacy in the canine XLHED model. Prior to the dosing of XLHED neonates in cohort 2, the DSMB also will have reviewed the safety and PK data from XLHED adult cohort 2 subjects dosed at the same 10 mg/kg/dose and the same 5 dose regimen.

In the core study, primary outcome measures will be safety, PK and immunogenicity. Secondary outcome evaluations of pharmacodynamics (PD)/efficacy will incorporate growth and development parameters, frequency of infections and hospitalizations, facial development as monitored by computerized recognition of XLHED-associated features, and assessments of ectoderm-related physiologic functions using technologies that minimize risk to this population. From 6 months onward (end of data collection in the Phase 2 core study), the EDI200-exposed infants will be enrolled in a long-term extension study with yearly safety and age-appropriate PD/efficacy evaluations.

Male siblings of study subjects, both affected and unaffected, will be offered enrollment in an accompanying natural history sub-study including a medical history questionnaire and a one-time, non-invasive evaluation of current clinical condition (without study drug administration, X-rays or blood draws). The results from these genetically related,

untreated siblings will provide comparative data for interpreting the clinical outcomes in treated study subjects.

SYNOPSIS

Title of Study	A Phase 2 open-label, dose-escalation study to evaluate the safety, pharmacokinetics, immunogenicity and pharmacodynamics/efficacy of EDI200, an EDA-A1 replacement protein, administered to male infants with X-Linked Hypohidrotic Ectodermal Dysplasia (XLHED)
Name of Company	Edimer Pharmaceuticals, Inc.
Name of Finished Product	EDI200
Name of Active Ingredient	EDI200
Protocol Number	ECP-002
IND Number	109262
EudraCT Number	2012-003561-17
Objectives	Primary Objectives • To assess the safety, pharmacokinetics and immunogenicity of EDI200 administered to XLHED-affected neonates Secondary Pharmacodynamic/Efficacy Objectives • To assess EDI200 pharmacodynamics/ efficacy in the treatment of XLHED-affected neonates • To compare clinical and medical history data obtained from untreated male siblings to that of the XLHED-affected neonate receiving study drug
Methodology	Phase 2 open-label, two cohort, dose-escalation study
Number of Subjects	• 6-10 XLHED-affected male neonates for study drug administration • Male siblings (XLHED-affected and unaffected) as historical controls
Diagnosis and Main Criteria for Inclusion	Male neonates documented by genetic diagnosis to carry an EDA mutation associated with XLHED, and their male siblings
Test Product Dose, Route of Administration	3 or 10 mg/kg/dose (IV)
Duration of Treatment	5 doses over 15 days

Pharmacodynamic/Efficacy Evaluations	• Growth and development • Infections and hospitalizations • Dentition • Facial development • Sweat gland number and function • Dry eye assessment • Thermoregulation • Skin biopsy for expression profile
Safety Evaluations	Safety laboratory blood tests, Vital Signs, Adverse Events
Pharmacokinetics Evaluations	Serial blood draws
Statistical Methods	The safety population will consist of all subjects who receive at least one dose of study medication. The PK population will consist of all subjects who receive at least one dose of study medication and have sufficient data points to obtain a plasma concentration by time profile. The PD/efficacy population will consist of all subjects who receive at least one dose of study medication and complete the follow-up assessments through at least month 2.

TIME AND EVENTS SCHEDULE – MULTI-DOSE EDI200 ADMINISTRATION

	Screening		Baseline	Treatment Phase										Follow-up Visits	Study Completion
	Prenatal[1] (Optional)	Postnatal[2] DOL 2 to DOL 12	DOL 2 to DOL 14[3]	TD 0	TD 1	TD 2	TD 4	TD 7	TD 11	TD 14	TD 15	TD 16	TD 21	Mon 2 & 4 of Life[4] (± 1 wk)	Mon 6 of Life[4] (± 2 wks)
Informed Consent	X	X	X												
Inclusion/Exclusion	X	X	X												
Genetic testing			X[5]												
Medical History	X	X[6]	X												
Safety Evaluations															
Physical Examination[7]			X	X	X		X	X	X	X	X		X	X	X
Safety Laboratory			X		X							X	X	X[8]	X
Immunogenicity			X									X		X[8]	X
Pharmacokinetic[9]			X	X	X	X				X		X	X	X[8]	X
PD/Efficacy															
Growth/Development			X											X	X
Dentition[10]			X												
Facial Development[11]			X												X
Sweat Assessments			X											X[8]	X
Dry eye Assessment			X											X[8]	X
Thermoregulation[12]			X										X		
Skin biopsy sample			X		X						X				
Study Drug				X			X	X	X	X					
Adverse Events/Con Meds[13]	X														

TIME AND EVENTS SCHEDULE – MALE SIBLINGS OF STUDY SUBJECTS

	Study Enrollment	Evaluation
	From date of 1st dose study drug administered to affected sibling	Prior to Study Completion for affected sibling
Informed Consent	X	
Inclusion/Exclusion Criteria	X	
Medical History	X	
Safety Evaluations		
Physical Examination		X
Weight, Height, Vital Signs		X
XLHED-associated Outcomes		
Growth/Development		X
Infections/Hospitalizations		X
Dentition		X[14]
Facial Development		X[15]
Sweat Assessments		X
Pulmonary function[16]		X
eNO level[17]		X
Dry eye Assessment[18]		X
Adverse Events & Con Meds	X	

1. Optional prenatal screening enrollment is from end of first trimester through delivery date
2. Newborn's screening window for study inclusion is through DOL #12
3. Baseline evaluations must be completed by DOL #14
4. Follow-up visits at 2, 4 and 6 months of chronologic age
5. In the Screening process, confirmation of subject EDA genotype is required from the family. Under Baseline Events, EDAR genotyping for the phenotype-modifying polymorphism EDAR V370A will be a standard assessment (Cluzeau et al., 2012) but is not required prior to study drug administration
6. Medical history encompasses antenatal and perinatal findings including antenatal ultrasound imaging of tooth buds if performed (Ulm et al., 1998)
7. A full physical examination will be conducted at baseline, day 21, months 2, 4, and 6. With the full physical examination will be the following quantitative assessments: weight, height, head circumference and vital signs (temperature, blood pressure, heart rate and respiratory rate). A brief physical examination will be conducted at treatment days 0, 1, 4, 7, 11, 14 and 15. The brief physical examination will include overall appearance (normal or abnormal and if abnormal why), skin appearance, cardiovascular, pulmonary and abdominal evaluation. With the brief physical examination will be weight and a set of vital signs (temperature, blood pressure, heart rate and respiratory rate). On dosing days vital signs will also be collected pre- and post dosing as described in section 3.3.8.
8. Studies to be performed at 2 months but not at the 4-month visit.
9. PK samples drawn pre-EDI200 dosing and post-end of infusion at approximately the following time points:

	Pre-Dose	Post-Dose							
		15 (±5) min	3 (±.5) hrs	8 (±1) hrs	18 (±2) hrs	24(±2) hrs	48 (±4) hrs	168(±8) hrs	Age 2 months (±1 wk) & 6 months (±2 wks)
D0 (dose 1)	X	X	X	X		X	X		
D14 (dose 5)	X	X	X		X		X	X	X

10. Baseline lateral jaw film only. Dental evaluation to be performed in the long-term extension study will minimize the use of dental radiographs, and allow for substitution of dental imaging obtained as part of the routine care of XLHED patients.

11. Digital analysis of non-invasive 2D facial photographs is a technology under development jointly by the Sponsor and a private company and is being explored as a tool for monitoring change in craniofacial appearance. The algorithm assesses the subject's facial structures in the neonatal period and continues through photographs taken in the extension study.
12. Thermoregulation assessment in the neonatal period is a well-documented procedure monitoring short-term temperature and vital sign response in a closed system (incubator). At an older age in the extension study, exercise-related thermoregulation will be assessed.
13. Infections/hospitalizations as PD/efficacy endpoint will be captured through adverse events
14. No dental radiographs will be taken as part of this sibling sub-study. Subjects will be asked to provide copies of recent dental X-rays from an outside source.
15. Frontal and lateral facial photographs to be taken and baby picture (age up to 1 month) to be collected if available
16. Minimum age 5 years for pulmonary testing
17. Minimum age 4 years for eNO assessment
18. A more comprehensive dry eye assessment will be performed in children as opposed to the neonates

LIST OF ABBREVIATIONS

Abbreviation	Definition
2D	Two Dimensional
ADL	Activities of Daily Living
AE	Adverse Event
AUC	Area Under the Curve
BSID	Bayley Scales of Infant Development
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTGF	Connective Tissue Growth Factor
DDST	Denver Development Screening Test
DOL	Day of Life
DSMB	Data Safety Monitoring Board
EDA	Ectodysplasin A
EDA-A1	Ectodysplasin protein A1
EDAR	Ectodysplasin-A1 Receptor
EDC	Electronic Data Capture
eCRF	Electronic Case Report Forms
eNO	Exhaled Nitric Oxide
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
Lgr5	Leucine-Rich G-Protein Coupled Receptor
MedDRA	Medical Dictionary for Regulatory Activities
NCD	Nonclinical Document
NCI	National Cancer Institute
NOAEL	No Adverse Effect Level
OSDI	Ocular Surface Disease Index
PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetic
RNA	Ribonucleic Acid
SAE	Serious adverse event
Shh	Sonic Hedgehog

SUSAR	Suspected Unexpected Adverse Reaction
TD	Treatment Day
XLHED	X-Linked Hypohidrotic Ectodermal Dysplasia

PI AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

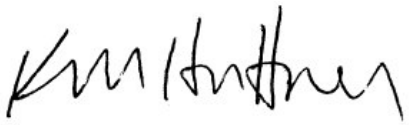
I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the conduct of the study.

PI's Signature* Date

Name of PI (Typed or Printed)

Institution Address*

Phone Number*



24JUNE2013

Sponsor's Medical Monitor Signature Date

Kenneth Huttner, MD, PhD

Name of Medical Monitor (Typed or Printed)

* If the address or phone number of the PI changes during the course of the study, written notification will be provided by the PI to the Sponsor and will not require protocol amendment(s).

1 BACKGROUND

XLHED, the most common of the ectodermal dysplasias, is caused by inherited defects in the ectodysplasin (EDA) gene that disrupt synthesis and/or function of the primary translational product EDA-A1 (www.ncbi.nlm.nih.gov/omim). In normal development, EDA-A1 acts as an ectoderm signaling molecule that binds specifically to the EDA-A1 receptor (EDAR) triggering initiation and maturation of ectoderm appendages into sweat and secretory glands, tooth buds and hair follicles. The absence of normal EDA-A1 expression results in sweat and secretory gland hypoplasia predisposing XLHED-affected infants to serious and potentially life-threatening hyperthermia and pneumonia (Clarke et al., 1987). XLHED-affected children surviving infancy face a host of life-long ectoderm-related clinical conditions including failure to thrive, oligodontia and misshapen teeth, mid-face hypoplasia, eczema, chronic dry eyes, asthma, respiratory infections, sinusitis and chronic nosebleeds. As is the general case with X-linked disorders, XLHED-affected males are more consistently and severely affected, while XLHED-affected females have a more variable phenotype.

There are no therapies currently available for XLHED that prevent or correct the underlying abnormalities of ectoderm-derived structures. In two genetically confirmed animal models of XLHED, systemic administration of recombinant EDA-A1 (EDI200) in the prenatal (mice) or postnatal (newborn mice and dogs) settings corrected many of the defects in ectoderm development resulting in a significant and sustained improvement in the health of the treated animals (Gaide and Schneider, 2003; Casal et al., 2007). To date, data in both species has demonstrated a restricted efficacy window that closes after the first several weeks of postnatal life (Gaide and Schneider, 2003; Edimer Study NCD-200-11-005). This is consistent with the well-studied timeframe for ectoderm appendage development, and supports the clinical development of EDI200 as a therapeutic to be administered to XLHED-affected patients in the newborn period or earlier.

1.1 Rationale for Study

Study Drug - EDI200 is a fully humanized EDA-A1 replacement molecule designed for parenteral administration, comprising the human IgG1 Fc sequence linked to the human EDA-A1 receptor-binding domain. The N-terminal Fc receptor portion of the EDI200 molecule serves to facilitate and stabilize the intermolecular associations required for EDAR binding, as well as providing a potential mechanism for fetal delivery (Miller, 2003). Through its unique design, EDI200 retains the EDA-A1 receptor specificity as evidenced by the targeted phenotype response in preclinical XLHED models (Gaide and Schneider, 2003; Casal et al., 2007; Mauldin et al., 2009).

Safety and PK data in Adults - Following discussions with the FDA regarding the clinical development plan for EDI200 in a pediatric indication; a Phase 1 study in XLHED-affected adults was initiated (NCT01564225, www.clinicaltrials.gov) to develop human safety and PK data in anticipation of dosing XLHED-affected neonates. Selecting XLHED-affected adults for

the Phase 1 study provided a genetic and biologic relevance to XLHED-affected neonates. Enrolling adult XLHED-affected males and females: (1) supported dosing of male XLHED neonates in the current trial; (2) provided data for the possibility of dosing XLHED-affected female neonates; and (3) initiated the collection of data necessary to support a future trial of maternal EDI200 administration. Identical dosage (mg/kg) and dosing regimens are planned for the adult and neonate XLHED studies.

Neonate Dosing Strategy: Age at Dosing Initiation; Dosing Regimen; Starting Dose

Age at Dosing Initiation – In both the mouse and dog XLHED models; early postnatal administration was associated with correction of clinically relevant abnormalities. Based primarily on the multi-dose dog data, study drug administration in this protocol is targeted to begin between day-of-life (DOL) #2 and DOL #14 (Edimer Study NCD-200-11-005).

Dose Regimen - The EDI200 dosing regimen proposed for the Phase 2 XLHED neonate study is a single course consisting of 5 doses administered at 2 doses/week. This regimen is based on results from the dog XLHED model which is most comparable to the human condition in developmental maturity at birth and in health-related endpoints (Casal et al., 2007; Edimer Study NCD-200-11-004). The 2-dose/week-regimen was incorporated into the GLP toxicology studies as well (Edimer Studies 1800-009 and 1800-010).

Starting Dose – No study-drug related adverse effects were observed at the highest EDI200 dose tested in both mouse and dog neonatal GLP toxicology studies, confirming a NOAEL of ≥200 mg/kg/dose (1800-009; 1800-010). Consistent with FDA guidelines for Maximum Starting Dose in Initial Clinical Trials, and incorporating a conservative approach to dosing in this vulnerable population, the first cohort of XLHED neonates will receive EDI200 at 3 mg/kg/dose IV, 0.015 x neonatal NOAEL (factor of 1/66). In the dog XLHED efficacy studies, dosing at 3 mg/kg/dose was associated with partial efficacy, which was enhanced significantly in animals receiving 10 mg/kg/dose (Edimer Study NCD-200-11-004). Safety and PK data from the Phase 1 adult study cohort treated with EDI200 at 3 mg/kg/dose x 5 doses over 15 days was reviewed by the DSMB with no reported study drug-related adverse events.

In the Phase 2 neonate study, the DSMB will review safety and PK data from neonate cohort 1, and in the absence of safety concerns, neonates will then be enrolled in cohort 2 and dosed at a pharmacologic half-log increase to EDI200 10 mg/kg/dose IV, equivalent to 0.05 x the neonatal NOAEL (factor of 1/20). Safety and PK data from the Phase 1 adult cohort 2, having received EDI200 at the same dose and the same dosing regimen, also will be reviewed by the DSMB prior to initiating dosing in neonate cohort 2. The dose for XLHED neonate cohort 2 is anticipated to maximize postnatal EDI200 efficacy based on the dog XLHED results (Edimer Study NCD-200-11-004).

Cohort enrollment - The Phase 2 neonate XLHED study is designed to enroll two cohorts of at least 3 subjects each (cohort size determined by rate of enrollment and sponsor discretion),

consistent with the practical aspects of study enrollment in ultra-rare orphan disorders and the unique challenge of enrolling newborns. Enrollment and dosing of all subjects in neonate cohort 1 (3 mg/kg/dose) will be completed and reviewed prior to initiating dosing of subjects in neonate cohort 2 (10 mg/kg/dose).

Primary objectives - Safety labs, physical examination, vital signs, adverse events and concomitant medications, immunogenicity, and PK will be documented as outlined in the Time and Events schedule. The schedule for PK sampling, based on the preclinical and Phase 1 adult XLHED dosing results, incorporates a sparse sampling approach to limit the frequency and volumes of neonatal blood draws. The proposed PK sampling maximizes data collection for determining both the AUC and Cmax.

Pharmacodynamic/efficacy objectives - PD/efficacy endpoint assessments relevant to the biology and pathophysiology of XLHED are incorporated into the study design as outlined in the Time and Events:

- *Clinical endpoints* - growth and development (including feeding history), infections and hospitalizations (captured under adverse events).
- *Imaging assessments* - diagnostic dental radiographs (the post-treatment dental X-rays will be incorporated into the long-term extension study and hence are not described further in this protocol), antenatal ultrasound results for tooth bud development (if available as part of Obstetric care, documented in the Medical History), pre- and post-treatment facial photographs to assess changes in craniofacial features associated with XLHED and its correction.
- *Clinical biomarkers* - sweat duct number and induced sweat volume, thermoregulation and dry eye evaluation.
- *Molecular biomarkers* - skin biopsy for expression profile.

All affected and unaffected male siblings of study subjects will be offered enrollment in a natural history sub-study evaluating the medical history and clinical condition of genetically related, untreated comparators for the study subjects.

Study Duration - Total study duration for each subject receiving study drug will be approximately 6 months, including a treatment and safety/efficacy monitoring period. A long-term extension study for all subjects receiving study drug will continue safety and PD/efficacy evaluations. Study duration for male siblings in the sibling sub study will be 1-2 days.

2 OBJECTIVES

2.1 Primary Objectives

To assess the safety, pharmacokinetics and immunogenicity of EDI200 administered to XLHED-affected neonates

2.2 Pharmacodynamic/Efficacy Objectives

- To assess the pharmacodynamics/efficacy of EDI200 administered to XLHED-affected neonates
- To compare clinical data and medical history obtained from untreated male siblings to that of the XLHED-affected neonates receiving study drug

3 STUDY DESIGN

3.1 Multi-Dose EDI200 Administration

3.1.1 *Brief Description and Rationale for Study Design*

X-linked hypohidrotic ectodermal dysplasia (XLHED) is a disorder of ectoderm development associated with EDA gene mutations that lead to a deficiency of the ectoderm signaling protein EDA-A1. EDI200 is a fully humanized EDA-A1 replacement molecule under development as a novel therapeutic for XLHED. In two XLHED animal models, a single course of perinatal EDI200 administration resulted in a substantial correction of abnormalities in ectoderm development and a significant improvement in the health of the treated animals (Gaide and Schneider, 2003; Casal et al., 2007). These preclinical findings support the clinical development of EDI200 as a therapeutic to be administered to XLHED-affected patients in the neonatal period or earlier.

The open-label Phase 2 study of EDI200 administered to XLHED-affected neonates will enroll 6-10 subjects in two sequential cohorts. Each study subject will have documentation of an EDA gene mutation. Cohorts will be enrolled sequentially, i.e. the first subjects will all be enrolled in cohort 1, and only after cohort 1 safety evaluation by the DSMB will subjects be enrolled in cohort 2 for dosing at a higher level. Final cohort size will be determined by subject and site availability, with at least 3 subjects per cohort.

The EDI200 dose for subjects in cohort 1 is 3 mg/kg/dose, consistent with the FDA Guidelines for Maximum Safe Starting Dose in Initial Clinical Trials based on the neonate NOAEL of $\geq$200 mg/kg/dose. This dose is anticipated to be associated with partial efficacy based on the dog XLHED studies. Safety laboratory results will be available to the DSMB in real time, and a formal DSMB safety and PK review will occur following completion of dosing in cohort 1. Additionally, the DSMB will have available to it safety and PK data from all XLHED-affected adult subjects from the Phase 1 adult safety study (NCT01564225, www.clinicaltrials.gov). In the absence of a safety signal or PK concern from DSMB review, XLHED neonates in cohort 2 will be dosed at 10 mg/kg/dose, a half-log pharmacologic increase to a dose anticipated to maximize clinical benefit based on the XLHED dog studies.

Primary outcome measures for all subjects will be safety, PK and immunogenicity. Study duration is 6 months with all subjects rolling over into a long-term extension study providing yearly evaluations. Pharmacodynamic/efficacy objectives in the Phase 2 neonate study will be limited by the timeline for ectodermal development that often exceeds 6 months, e.g. dentition. Therefore, several of these endpoints will be incorporated into the extension study protocol. There will be assessment of the following: (1) endpoints relevant to the common clinical findings in XLHED using age-appropriate technologies, e.g. growth and development, infections and hospitalizations, sweat duct counts and stimulated sweat production, pre-treatment dentition, and thermoregulation; (2) change from baseline in craniofacial structures

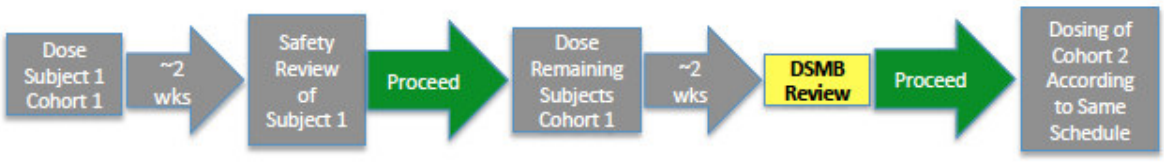
using a non-invasive facial recognition software program based on subject digital facial photographs (Appendix 1); and (3) change in molecular expression profile using skin biopsy samples obtained pre- and post-study drug exposure.

3.1.2 *Starting and Target Dose/Dosing Regimen*

The proposed starting dose is consistent with the FDA Guidelines for Maximum Safe Starting Dose in Initial Clinical Trials, based on the neonate GLP toxicology studies in two species that demonstrated a NOAEL of ≥200 mg/kg (MPI Study 1800-009 and 1800-010). Cohort 1 subjects will be dosed with EDI200 at 3 mg/kg/dose IV, 0.015 x neonate NOAEL (factor of 1/66). The proposed dosing regimen of 2 doses/week x 5 doses, beginning within the first 2 weeks of life, is supported by the dosing regimen in the GLP toxicology studies. This dose and dosing regimen is in the range of anticipated partial efficacy in the dog XLHED model, considered the most relevant species for endpoint assessment.

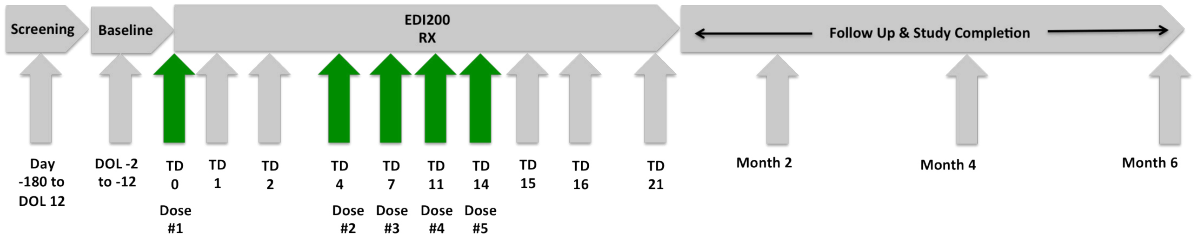
Prior to enrolling subjects in neonate cohort 1, the DSMB reviewed safety and PK data from cohort 1 in the Phase 1 XLHED study (NCT01564225) where adult XLHED subjects were administered EDI200 at the same dose (3 mg/kg/dose) and dosing regimen (5 doses total at 2 doses/week). No study drug-related adverse events were reported. In neonate cohort 1, the first subject enrolled will complete dosing followed by a ~2-week safety review. If no safety concerns are observed, the remaining cohort 1 subjects will begin dosing. Dosing for individual subjects will be on a mg/kg basis.

Once all subjects in neonate cohort 1 have received their IV dosing, the DSMB will review safety and PK data. In the absence of safety concerns following DSMB review of cohort 1 data, neonates in cohort 2 will be dosed at a pharmacologic half-log increase to 10 mg/kg/dose, 0.05 x neonate NOAEL (factor of 1/20), following the same 5-dose regimen (see figure below). The dose and dosing regimen for neonate cohort 2 is in the range anticipated to maximize postnatal efficacy based on results from the dog XLHED model. Dosing of subjects in cohort 2 is sequential as described in cohort 1. Subject enrollment and cohort initiation will be according to the following schedule:



The study will be conducted in age-appropriate clinical facilities by medical staff with appropriate levels of training and expertise and an understanding of the investigational medicinal product, its target and mechanism of action. There will be immediate access to facilities for the treatment of medical emergencies including an Intensive Care Unit.

The study timeline and visit dates for each subject are as follows:



3.1.3 *Screening*

A family with a male fetus/newborn with a clinical suspicion of XLHED may inquire to receive study information by phone, email or directly at a study site (also available on www.clinicaltrials.gov). If the family then wishes to be considered for study participation, they have the following options:

1. Prenatal Screening Enrollment (optional): the family of a male fetus at risk for XLHED may provide Informed Consent (ICF1) for data collection to begin in order to evaluate eligibility for newborn EDI200 treatment (see Sections 3.3.1 and 3.3.2). Entering the screening process early will allow for discussion and planning to minimize the potential family disruption that is likely to accompany early postnatal transfer to the study site if the subject is to be enrolled in the treatment protocol. The language of ICF1 will state clearly that once all Inclusion/Exclusion (I/E) criteria are met, an additional Informed Consent (ICF2), obtained postnatally, will be required in order to enroll the XLHED-affected neonate into the treatment portion of the study. The enrollment window for treatment encompasses the period from DOL #2 through DOL #12 (allowing a minimum of two days for transfer to the study site and baseline assessments prior to DOL #14, the last day study drug dosing can be initiated).

2. Postnatal Screening Enrollment: in the absence of Prenatal Screening Enrollment, the family of a male newborn at risk for XLHED may provide Informed Consent (ICF1) for data collection to begin in order to evaluate eligibility for the newborn EDI200 treatment (see Sections 3.3.1 and 3.3.2). The language of ICF1 will state clearly that once all Inclusion/Exclusion (I/E) criteria are met, an additional Informed Consent (ICF2) will be required in order to enroll the XLHED-affected neonate into the treatment portion of the study. The enrollment window for treatment encompasses the period from DOL #2 through DOL #12 (allowing a minimum of two days for transfer to the study site and baseline assessments prior to DOL #14, the last day study drug dosing can be initiated).

A key inclusion criterion for the treatment protocol is verification of the XLHED diagnosis through EDA mutation testing. As part of the screening process, genetic testing results may be provided by the family to the study site via a secure and confidential method including the option for electronic transmission. If genotyping confirmation is not available at the time of

Screening Informed Consent, the families of prospective subjects will be referred to resources available to facilitate rapid genotype testing at an accredited laboratory.

Families may be considering delivery at a clinical study site to facilitate treatment of their XLHED-affected son as soon as possible after birth. Any such decision is outside of this protocol and would be a private matter between the family, their health care providers, their insurance company, and the delivery service at the study site. Delivery at the study site would not commit the family to have their newborn participate in the treatment protocol, nor would it commit the PI and study site to enroll the XLHED-affected male neonate unless and until he met all the required I/E criteria and a treatment Informed Consent (ICF2) was signed by both parents (if reasonably available).

If the XLHED-affected neonate meeting inclusion/exclusion criteria is not born at the study site, the study team will assist in and cover all reasonable expenses associated with his transfer to the site. If medical transport is required, this will occur under specific Informed Consent (ICF-T) requiring signatures of both parents (if reasonably available). The window for transfer to the study site must allow for the neonate to complete Baseline evaluations in a timely manner prior to DOL #14.

3.1.4 *Baseline*

Baseline evaluation will begin with confirmation of treatment inclusion/exclusion criteria and documentation of relevant family, pregnancy and neonatal medical history. Baseline assessments of the XLHED-affected male infant as described below are to be completed prior to first dose study drug. To date, there is little data published describing evaluation techniques for XLHED patient in the newborn period. The Sponsor has experience with using the novel, minimally invasive technologies that are incorporated into this study protocol (www.edimerpharma.com/Publications and News/Publications and Abstracts)

In this Phase 2 protocol, baseline assessments of the neonate study subjects will serve three purposes. First, they will verify the general health of the XLHED-affected infant including documentation of developmental status and full physical examination. Second, blood samples will be collected for pre-treatment safety laboratory values, documentation of the absence of EDI200 and anti-EDI200 antibodies, and genotyping of the EDAR V370A polymorphism that has the potential to modify the XLHED-phenotype. Third, they will document pre-treatment ectoderm status related to EDA-A1 deficiency, including sweat duct number, induced sweat volume, presence/absence of dentition on lateral jaw radiograph, dry eyes, digital 2D facial photograph for XLHED facial appearance, thermoregulation imbalance and skin biopsy for expression profile.

3.1.5 *Treatment Period*

The subject will be admitted to the study site during the entire dosing period. The schedule of events for this portion of the study is presented in the Time and Events Table. In each cohort, the first subject enrolled will complete the 15-day dosing period and undergo monitoring for an additional week at the study site. The site and Sponsor Medical Monitors will then review all AE and safety laboratory data. In the absence of any clinically significant AE's the remaining cohort subjects may begin dosing. It is anticipated that the timeframe from last dose of the first cohort subject through AE review will be approximately 2 weeks.

Each subject will be administered 5 doses of EDI200, administered IV on Treatment Days (TD) 0, 4, 7, 11 and 14, with vital sign monitoring during and for 24 hours following each dose of study drug. The Treatment Day for doses two through five may be $\pm$1 day, but doses must be at least 48 hours apart. Subjects in cohort 1 will be dosed at 3 mg/kg/dose calculated on Baseline weight.

On TD 0, subjects will have the following evaluations performed prior to dosing: brief physical exam, AE and concomitant medication assessment. Subjects will be administered dose 1 of study drug with vital sign monitoring during and for 24 hrs post-dose. Full details of the vital sign monitoring plan are described in Section 3.3.8. Sparse PK sampling time points post-dosing are described in Section 4.5.2.

On TD 1, subjects will have the following evaluations performed: brief physical exam, AE and concomitant medication assessment, safety laboratories, PK sampling and skin biopsy for expression profile (both approximately 24-hour post dose 1).

On TD 2, subjects will have the following evaluations performed: AE and concomitant medication assessment and PK sampling (approximately 48-hour post dose 1).

On TD 4, subjects will have the following evaluations performed prior to dosing: brief physical exam, AE and concomitant medication assessment. Subjects will be administered dose 2 of study drug with vital sign monitoring during and for 24 hrs post-dose.

On TD 7, subjects will have the following evaluations performed prior to dosing: brief physical exam and AE and concomitant medication assessment. Subjects will be administered dose 3 of study drug with vital sign monitoring during and for 24 hrs post-dose.

On TD 11, subjects will have the following evaluations performed prior to dosing: brief physical exam and AE and concomitant medication assessment. Subjects will be administered dose 4 of study drug with vital sign monitoring during and for 24 hrs post-dose.

On TD 14, subjects will have the following evaluations performed prior to dosing: brief physical exam and AE and concomitant medication assessment, and PK sampling. Subjects will

be administered dose 5 of study drug with vital sign monitoring during and for 24 hrs post-dose. Sparse PK sampling time points post-dosing are described in Section 4.5.2.

On TD 15, subjects will have the following evaluations performed: brief physical exam, AE and concomitant medication assessment, and a skin biopsy obtained approximately 24 hours after administration of the last dose of study drug.

On TD 16, subjects will have the following evaluations performed: AE and concomitant medication assessment, safety laboratories, immunogenicity sampling, and PK sampling (approximately 48-hour post dose 5).

On TD 21, subjects will have the following evaluations performed: full physical examination, AE and concomitant medication assessment, post-treatment thermoregulation assessment, safety laboratories and PK sampling (approximately 168-hour post dose 5).

The remainder of the study procedures through Month 6 are described in the post-treatment section, Section 3.1.6.

Dose escalation in XLHED neonate cohort 2 will not occur until a review of safety and PK data from XLHED neonate cohort 1 has been completed by the DSMB, approximately three weeks after the last subject is dosed in cohort 1. Assuming no safety or PK concerns following DSMB review, subjects in XLHED neonate cohort 2 will be dosed with EDI200 at 10 mg/kg/dose IV, a pharmacologic half-log increase. As part of the safety-monitoring program, prior to dosing subjects in neonate cohort 2 the DSMB will have reviewed safety and PK data from adult cohort 2 in the Phase 1 adult XLHED study where subjects received EDI200 at the same dose (10 mg/kg/dose) and dosing regimen (5 doses total at 2 doses/week).

3.1.6 *Post-Treatment Follow Up*

The post-treatment visits at Months of Life 2, 4 and 6 are designed to capture safety, immunogenicity and PD/efficacy data at appropriate timepoints following study drug exposure. In addition, PK data will be collected at Months of Life 2 and 6 visits. The post-treatment frequency of visits to the study site represents a balance between the acquisition of informative data and minimizing the travel stresses for the infant subject and his family. These evaluations will not supplant the subject's normal well-child care visits and immunizations by his primary care provider.

At Month 2 of life, subjects will have the following evaluations: full physical exam, AE and concomitant medication assessment, safety laboratories, PK and immunogenicity sampling, and PD/efficacy evaluations including growth and development, induced sweating and sweat duct imaging and dry eye evaluation. Expected stay at the study site location (i.e. within the vicinity of the study site) is 1-2 days.

At Month 4 of life, subjects will have the following evaluations: full physical exam, AE and concomitant medication assessment, and PD/efficacy evaluations including growth and development. Expected stay at the study site location (i.e. within the vicinity of the study site) is 1-2 days.

At Month 6 of life, subjects will have the following evaluations: full physical exam, AE and concomitant medication assessment, safety laboratories, PK and immunogenicity sampling, and PD/efficacy evaluations including growth and development, induced sweating and sweat duct imaging, dry eye assessment and digital facial photographs. Expected stay at the study site location (i.e. within the vicinity of the study site) is 1-2 days.

The conclusion of the core study is defined as the last visit of the last participant.

3.2 XLHED-Affected and Unaffected Male Siblings of Study Subjects

All male siblings (including multiple male siblings of a singe neonate) of enrolled XLHED-affected neonates will be offered the opportunity to participate in a non-invasive evaluation providing historical control data for this open-label study. The technologies involved will be modeled on the core study evaluations, with the exception that no X-rays will be taken; no blood draws and no tissue sampling will be involved. The evaluations will take place at the study site and will include Informed Consent and Assent, if applicable, medical history, physical examination, vital signs including weight and height, digital facial photographs (frontal and lateral), growth and development assessments, induced sweating and sweat duct imaging, pulmonary function testing and eNO levels when age-appropriate (see Time & Events Schedule), dry eye evaluation and dental examination. Siblings will be asked to provide copies of their most recent dental radiographs. Expected stay at the study site location (i.e. within the vicinity of the study site) is 1-2 days.

3.3 Study Subjects

This Phase 2 study will enroll 6-10 XLHED-affected male neonates for study drug administration, and includes the optional enrollment of all male siblings, both affected and unaffected, for non-invasive evaluations.

3.3.1 *Inclusion Criteria*

Subjects for study drug administration must meet all of the following criteria to be enrolled:

1. Male with genetic confirmation of an XLHED diagnosis.
2. Subject must be at least 48 hours age and no older than 14 days.
3. Subject will have reached term (defined as 37 weeks gestation or older) prior to receiving first dose study drug.

4. Written informed consent of both parents (if reasonably available) must be obtained for treatment of their XLHED-affected male infant.
5. Neither mother nor the XLHED-affected male infant known to have received an investigational study drug in the 9 months prior to study subject enrollment in this study.
6. No major medical issues that the PI considers a contraindication to participation.

Male siblings of subjects receiving study drug must meet all of the following criteria to be enrolled in the natural history sub-study (no age limit involved):

1. Provide written informed consent/assent.
2. A full or half-sibling of a study subject where the study subject has received at least one dose of study drug in the Phase 2 XLHED Neonate Study and has not yet completed the study.
3. No major medical issues that the PI considers a contraindication to participation.

3.3.2 *Exclusion Criteria*

Subjects for study drug administration who meet any of the following criteria cannot be enrolled in this study:

1. Medically significant postnatal complications or congenital anomalies outside of those considered associated with the diagnosis of XLHED.

Male siblings of subjects receiving study drug who meet any of the following criteria cannot be enrolled in the natural history sub-study:

1. Known hypersensitivity to pilocarpine or pilocarpine-like muscarinic agonists.
2. Known hypersensitivity to lidocaine or lidocaine-like agents.
3. Presence of pacemaker.
4. Subjects who are not able or are not willing to comply with the procedures of this protocol.
5. Subject has a condition, which in the opinion of the PI would not allow for safe conduct of the study.

3.3.3 *Withdrawal or Removal of Subjects from the Study*

Study subjects/guardians may elect to discontinue study subject participation and withdraw from the study at any time without prejudice. The PI or Sponsor may withdraw a subject from participation in this study for any of the following reasons:

- A protocol violation occurs,
- The subject is not compliant with study procedures,
- A serious or intolerable adverse event occurs,
- The Sponsor or PI terminates the study, or
- The subject/guardian requests to be discontinued from the study.

A discontinuation occurs when an enrolled subject ceases participation in the study prior to completion of the protocol, regardless of the circumstances. The PI will determine the primary reason for discontinuation, and it will be recorded in the case report form and in the subject's research record. A discontinuation must be reported immediately to the Sponsor if it is due to a serious adverse event. The PI will provide or arrange for appropriate follow-up for such subjects (if required), and document the course of the subject's condition. In all cases of subject discontinuation, an attempt should be made to obtain the End-of-Study evaluations at their last study visit.

3.3.4 *Subject, Cohort or Study Suspension/Termination*

The Sponsor and/or the DSMB have the right to close this study at any time for safety or administrative reasons, although this should occur only after consultation between involved parties. The IRB/IEC and all relevant local National Competent Authorities must be informed.

3.3.5 *Subject Stopping Criteria*

- All AE and safety laboratory results will be available to the Medical Monitor, PI and DSMB in real time.
- For any Grade 2 or 3 adverse event (AE) defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v4.0; Appendix 2) that is deemed possibly, probably or definitely related to study drug treatment, individual subject dosing will be held pending review and recommendations of the Medical Monitor.
- If a subject misses a single dose and then is restarted, that dose will not be made up but all subsequent doses will be administered on schedule.
- If a subject misses two consecutive doses then dosing will not be restarted, but all study follow-up visits will occur as originally scheduled.

3.3.6 *Cohort Stopping Criteria*

The study design has only one cohort being dosed with study drug at any given time. Dosing of all subjects within a cohort will be suspended for:

- Two or more individuals develop a Grade 2 or 3 AE in a similar system organ class deemed possibly, probably or definitely related to study drug treatment (CTCAE v4.0), or
- For any Grade 4 adverse event (classified as severe or life-threatening) or a serious adverse event (SAE), regardless of drug-relatedness.

In the case where cohort dosing has been suspended, DSMB review of the AEs with the Medical Monitor, study PI and Sponsor will be required prior to discussing with a subject's family the option of restarting study drug or to enrolling additional subjects in the cohort. Missed doses will not be made up. Any subject missing two consecutive doses will not be restarted on treatment, will not be considered to have completed the dosing regimen, but will have all study follow-up visits as originally scheduled. If the DSMB safety review concludes that cohort dosing may continue, an additional subject may be added to the cohort for each subject that does not complete the dosing regimen.

In the case where a DSMB safety review concludes that a cohort should not continue dosing, no additional doses will be administered to subjects in that cohort, no additional subjects will be enrolled in that cohort, and all follow-up visits for enrolled subjects will occur as originally scheduled. The Sponsor will notify both the relevant National Competent Authorities and the local IRB/IEC of the action taken. The scheduled dose escalation cohorts will be suspended, although a more conservative dose escalation strategy may be considered for a subsequent cohort, requiring DSMB, relevant National Competent Authorities and study site IRB/IEC approval.

3.3.7 *Study Stopping Criteria*

The Sponsor and/or the DSMB have the right to close this study at any time for safety or administrative reasons, with timely notification of the relevant National Competent Authorities.

Permanent halting of dosing in any cohort by the DSMB related to safety concerns will trigger an automatic review of study termination by the DSMB in communication with the Medical Monitor, study PI, and Sponsor. If it is determined that study dosing should be terminated, all follow-up visits will occur as originally scheduled for subjects having received one or more doses of study drug. Study Sponsor assumes responsibility for reporting premature study termination to all regulatory authorities and institutional review boards.

Should the study be closed prematurely, all study materials (except documentation that has to remain stored with the PI) must be returned to the Sponsor. The PI will retain all other documents until notification given by the Sponsor for destruction.

3.3.8 *Treatment*

EDI200 study drug will be provided as a sterile solution for intravenous infusion in 3 ml glass vials, approximately 2.1 ml/vial at a concentration of approximately 5 mg/ml. Vials will be labeled according to local regulations and Sponsor standards. All study drug supplies should be stored frozen at -60 °C to -90 °C.

Dosing of EDI200 will vary by cohort. Study drug administration will be as follows:

Cohort	Number of subjects	Dose	Number of Doses	Study Day of Administration
Cohort 1	3-7	3 mg/kg	5	0, 4, 7, 11, 14
Cohort 2	3-7	10 mg/kg	5	0, 4, 7, 11, 14

The weight used to calculate study drug dose will be the subject's Baseline weight for all doses. If during the treatment period a subject experiences a change in weight of >10% from Baseline, the PI(s) and the Medical Monitor will review the option of adjustments to the subject's dosing.

EDI200 will be **thawed to room temperature** on the day of dosing, pooled in syringe(s) and administered via a syringe pump infusion system. The study drug shall be administered by slow IV infusion over at least 30 min, not to exceed 5 ml/kg/hour or 8.5 mg/min EDI200, in order to minimize the risk of infusion-related AE (refer to Investigational Brochure, Section 6.2). For more information on the preparation of EDI200 see the Pharmacy/Investigator Manual.

Examples are shown in the table below.

Subject Weight	EDI200 Dose (mg/kg)	Total Dose EDI200	EDI200 Conc (mg/ml)	Vol	Vol/kg	Minimum Infusion Time	ml/kg/ hr	EDI200 mg/min
3 kg	3	9 mg	5	1.8 ml	0.6 ml/kg	0.5 hrs	1.2	0.3
3 kg	10	30 mg	5	6 ml	2.0 ml/kg	0.5 hrs	4	1.0
4 kg	3	12 mg	5	2.4 ml	0.6 ml/kg	0.5 hrs	1.2	0.4
4 kg	10	40 mg	5	8 ml	2.0 ml/kg	0.5 hrs	4	1.3
5 kg	3	15 mg	5	3 ml	0.6 ml/kg	0.5 hrs	1.2	0.5
5 kg	10	50 mg	5	10 ml	2.0 ml/kg	0.5 hrs	4	1.7

During study drug administration and for 24 hrs following infusion the subject will have continuous heart rate and respiratory rate monitoring. A full set of vital signs including temperature, blood pressure, heart rate and respiratory rate will be documented on the following schedule:

- Pre dosing - a single set of vital signs within 1 hour of initiating dose infusion
- Post dosing:
    - 15 min after end of infusion,
    - 1 hr and 4 hrs after end of infusion,
    - then q4 hrs up to 24 hrs after end of infusion

If the unit in which the subject is receiving study drug requires additional monitoring, then that data will be added to the subject's record.

The intravenous site will be assessed for patency and signs of local irritation prior to the start of the infusion, every 30 minutes during infusion, and at the end of study drug infusion.

Doses 2-5 are scheduled for study days 4, 7, 11 and 14 respectively in both cohorts. If the subject is unable to be dosed on the specified day, a window of $\pm$24 hours is acceptable. However, there must be a minimum of two days between any two doses. The calendar date and 24-hour clock time of the beginning and end of each infusion will be recorded on the CRF. The dates and timing of PK sampling around dose 5 will be adjusted for any change in dosing schedule.

It is the responsibility of the clinical investigator to ensure that all study drug received at the site will be inventoried and accounted for throughout the study. Study drug must be handled strictly in accordance with the protocol and the container label and will be stored in a limited access area under appropriate environmental conditions. The investigator agrees neither to dispense the study drug from, nor store it at any site other than the study site locations agreed upon with the sponsor. Study drug should be dispensed under the direction of the investigator.

Study drug will be supplied only to subjects participating in the study. Study drug may not be relabeled or reassigned for use to other subjects. The dispensation and use of study drug must be documented on the Drug Accountability Form. Used and unused study drug must be available for verification by the sponsor's site monitor during on-site monitoring visits. The destruction or return to the sponsor of used or unused study drug will be approved by the sponsor and documented on the Drug Return Form.

4 STUDY EVALUATIONS

4.1 Medical Questionnaires

Two questionnaires are provided - one designated for the mother and XLHED-affected neonate (Appendix 3) and one designated for male siblings of an enrolled neonate (Appendix 4). The former includes family history related to XLHED, pregnancy, labor and delivery, and neonatal data. The latter includes general medical history with an emphasis on issues common to XLHED-affected males. This questionnaire will be used for both affected and unaffected male siblings.

4.2 Pharmacodynamic/Efficacy Evaluations

Assessment of PD/efficacy endpoints will be performed on all subjects. The Sponsor will provide any equipment and training required for assessments.

4.2.1 *Growth and Development*

Cross-sectional data in patient populations with hypohidrotic ectodermal dysplasia consistently reports poor growth in infancy, most commonly poor weight gain and feeding issues, and an elevated risk of abnormal development (Clarke et al., 1987; Motil et al., 2005; Blüschke et al., 2010). The growth assessments will consist of feeding history as well as measurements of weight, length, and head circumference taken at study visits as part of the physical examination and plotted on standardized growth curves for males. The initial physical examination will include assessment of standard developmental milestones, and will be augmented at Months 2, 4 and 6 by a validated, standard of care infant assessment tool. Examples of such tools include but are not limited to the Bayley Scales of Infant Development II (BSID-II) and III (BSDI-III) and the Denver Development Screening Test II (DDST II) (Black and Matula, 2000). Whichever tool is selected should be designed for down to age 2 months of life and should be used for all follow-up visits.

4.2.2 *Thermoregulation*

XLHED-affected neonates and infants have a well-documented abnormality of thermoregulation (heat intolerance) and as a consequence are at elevated risk for life-threatening hyperthermia under unmonitored conditions (Clarke et al., 1987; Blüschke et al., 2010). At present there are no validated genetic, clinical or physiologic markers that identify the level of risk for a given XLHED-affected patient. In this protocol, assessment of thermoregulatory risk for an XLHED-affected neonate will provide valuable information for the family in preparing for a safe transition to home. Additionally, demonstration in the long-term extension study of an improved and sustained thermoregulatory improvement may be a key efficacy element in the response to study drug. Thus it is a relevant and appropriate

evaluation in this protocol to assess thermoregulation of study subjects under closely monitored conditions with direct physician observation.

Thermoregulation reflects both sweat and insensible losses from the respiratory tract, both organ systems with compromised function in XLHED (Chawla et al., 2008; Clarke et al., 1987; Zankl et al., 2001; Casal et al., 2007; Seeliger et al., 2005). For term newborns placed inside a heated isolette, there is a wealth of validated clinical data on how to perform thermoregulation studies safely and what are the normal response parameters (e.g. Hey, 1975; Sjors et al., 1997; Stothers and Wagner, 1984; Sulyok et al., 1976). Healthy term babies reach the point of having to sweat to maintain body temperature at an isolette temperature of approximately 34°C. For thermoregulation assessment the study subjects will be placed unbundled in an isolette at a starting temperature of no more than 33°C in the ICU with continuous vital sign monitoring including respiratory rate, heart rate and body temperature. Isolette temperature will be held at the starting temperature for 0.5 hours for initial adaptation and baseline vital signs, following which it will be raised stepwise by 1-1.5°C every 30 minutes until reaching 36.5°C to assess infant response (Rutter and Hull, 1979). Total observation time is anticipated to be no more than 3 hours.

Strict stopping criteria will be in effect including: (1) a body surface temperature of $\geq$37.9°C (Rutter and Hull, 1979); (2) a noticeable change in behavior, e.g. uncontrolled crying; or (3) a sustained heart rate or respiratory rate outside of the normal range (HR 120-160 per minute; respiratory rate 40-60 per minute; Cloherty et al. 2004). With any of these changes or at the discretion of the study physician monitoring the assessment, the subject will be removed from the isolette to an unheated observation table until all vital signs and physical examination return to Baseline. Additional interventions are not anticipated, but will be at the discretion of the monitoring physician and the ICU staff.

In this exploratory endpoint, each subject's pre-dosing response to this short and controlled environmental challenge will be compared with the published literature and with the result of thermoregulation assessment after EDI200 dosing. Additional assessments of thermoregulation and heat tolerance are not standardized for ages 2-6 months but will be included as efficacy endpoints in the long-term extension study.

4.2.3 *Eccrine Structures*

4.2.3.1 Sweat Duct Density

Sweat duct density (number/cm^2) from at least two different sites on the soles of the feet (newborns and infants) or palms (siblings age $\geq$1 year) will be determined through analysis of images collected by direct visualization with an approved device, the Lucid VivaScope 1500 (www.lucid-tech.com). This technology has been tested in controls and XLHED-affected males from the newborn period to adulthood without complication (Dietz et al., 2013; Huttner et al., 2012; ECP-005 Clinical Study

Report). An adhesive ring will be placed on the subject's palm/sole to which the VivaScope will be attached via a magnetic lock. A series of photographs will be taken of an area approximately 6mm X 6mm. An individual trained in the use of this device will be involved in the acquisition of all images.

Up to two independent image readers trained in the reading of VivaScope images will interpret the images and provide sweat duct counts for inclusion with the study data. If there is a discrepancy in their counts of 10% or greater on an individual image, then both readers will reinterpret the same image and a final assessment made as an average of the repeat sweat duct counts. To account for growth during the study, all sweat duct counts will be adjusted for body surface area (Haycock et al, 1978).

4.2.3.2 Sweat Rate Testing

Sweat rate assessment following cholinergic stimulation is a technique used commonly in clinical trials as reported for the evaluation of distinct conditions including orthostatic hypotension, diabetes, growth hormone deficiency, Parkinson's disease, hypohidrosis, and Fabry's disease (Itoh et al., 2003; Low et al., 1983; Ramaswami et al., 2007). Maximal sweating on the volar lower arm surface of each subject will be induced by pilocarpine iontophoresis followed by sweat collection using the Macroduct Sweat Collection System developed primarily for sweat collection and analysis in the diagnosis of Cystic Fibrosis from the newborn period on (www.wescor.com). The Collection System consists of the Webster Sweat Inducer, Pilogel® Iontophoretic Discs and Macroduct Sweat Collectors. The Macroduct Sweat Collection System is approved for subjects of all ages including neonates (Mastella et al., 2000) and the manufacturer provides adequate directions for the device's use.

Pilogel® Iontophoretic Discs are unique gel reservoirs of pilocarpinium ions that are simple and safe to use in the iontophoretic stimulation of sweat. A Pilogel® disc is inserted into each of the recessed stainless steel electrodes, which are then attached to the subject. The Webster Sweat Inducer is activated by a start switch subsequently delivering a safe and optimal quantity of pilocarpine for gland stimulation (equivalent to five minutes iontophoresis at 1.5 mA) followed by an automatic, programmed stop.

Following completion of the pilocarpine iontophoresis the Webster Sweat Inducer electrodes and discs are removed from the subject, the application site is wiped once with alcohol, and a Macroduct Sweat Collector is placed over the site of one electrode. The Macroduct Sweat Collector is held in place for approximately 30 minutes using a Velcro Macroduct Strap. Sweat volume is determined from microliter markings on a collection coil diagram.

Individuals trained in the use of the Macroduct Sweat Collection System will be involved in both procedures and the acquisition of the data. The manufacturer of the iontophoresis device does report the rare occurrence (1 in 50,000) of small skin burns at the site of application, and physicians will be available on site to evaluate any adverse event occurrence.

4.2.4 *Pulmonary Function Testing and eNO levels*

Pulmonary function testing will be performed in the sibling sub-study on all subjects age 5 years and older at a laboratory experienced with pediatric subjects. Additionally, levels of exhaled nitric oxide (eNO) as an indicator of pulmonary inflammation will be quantified non-invasively with an age-group appropriate device in all siblings age 4 years and older.

4.2.5 *Dry Eye Assessment*

The eye examination will be performed by an ophthalmologist experienced in assessments of tear film and ocular surface in infants as well as children and adults. In newborns and infants, the examination will document the presence/absence of signs of infection and irritation, as well as a tear film break-up time. For children 5 years or older (sibling sub-study) the assessment will also include the Shirmer test for rate of tear production and the OCULAR SURFACE DISEASE INDEX© questionnaire (Appendix 5).

4.2.6 *Skin Biopsy*

Three mm diameter punch biopsies of skin will be obtained from the upper outer thigh area. Sites will follow their institutions standard practice with regard to biopsy procedure. The biopsy site may require absorbable suture(s). RNA isolated from the skin biopsies will be assayed in expression analyses to establish a biochemical response to EDI200 treatment in these EDA-deficient subjects. Genes to be evaluated include but are not are not limited to those involved in the EDA/EDAR pathway, e.g. EDAR, CTGF (connective tissue growth factor), Shh (sonic hedgehog) and Lgr5 (leucine-rich G-protein coupled receptor). For each study subject, comparisons will be made between the expression profiles obtained at Baseline, after the first and the last dose of EDI200.

4.2.7 *Dental Imaging/Examination*

The absence of tooth buds is a key confirmatory finding in phenotype assessment of an XLHED-affected neonate and can be determined from a lateral radiograph (Swischuk, 2003). Radiation exposure will be minimized in this study with a single lateral film at Baseline. Follow-up radiographs will be included in the long-term extension study for PD/efficacy documentation (first follow-up expected at age 2 years). Radiographs are the preferred

imaging modality as they detect tooth bud mineralization but do not require sedation in the infant.

The sibling sub-study includes a dental examination that is brief and age-appropriate involving an assessment of tooth count and tooth shape. No X-ray exposure will be involved.

4.3 Genetic Testing

To meet inclusion criteria for EDI200 administration, potential study subjects are required to have their XLHED diagnosis confirmed by genetic testing of the EDA gene and these test results relayed to the study site. EDA genetic testing itself is outside of the scope of this protocol. If requested, the families of prospective subjects in need of EDA genotyping will be referred to resources available to facilitate this testing. Consent from the family (written or verbal) will be obtained as part of the screening process to provide the study site with documentation of genetic testing results via a secure and confidential method including an option for electronic transmission.

It has been demonstrated that a polymorphism in the EDAR gene associated with increased activity may be associated with amelioration of some XLHED-symptoms (Cluzeau et al., 2012). As this has the potential to impact outcome measures, all participating neonates will be tested for this specific polymorphism, c.1540T>C, rs3827760, p.V370A. The testing may be performed on the prior DNA sample used for EDA genotype confirmation, although results are not required prior to the initiation of dosing.

4.4 Digital Facial Photographs

A facial recognition software algorithm is under development that will identify characteristics of XLHED-affected males as neonates, children and adults. The algorithm uses non-invasive 2D frontal photographs and will be used in this study to document the newborn facial appearance as well as changes in craniofacial appearance over time, including the long-term extension study. Facial frontal and lateral digital images will be obtained with a commercial camera, and all photographs will be anonymized prior to transmission for analysis to FDNA, the company developing the software algorithm (http://www.fdna.com).

4.5 Clinical and Safety Laboratory Evaluations

4.5.1 *Safety Laboratory Sampling*

Laboratory parameters measured at the study site will include a complete blood count (RBC, WBC, hemoglobin and hematocrit) with differential and platelet count, serum chemistries including glucose, electrolytes (Na, K, Cl, Ca), total protein and albumin, assessment of hepatic and renal function (BUN, serum creatinine, AST, ALT and alkaline phosphatase), and urinalysis (dipstick and microscopy). It will be the Principal Investigator's responsibility to assess laboratory parameters against local reference ranges and to assess the clinical significance of any out-of-range values.

4.5.2 *Pharmacokinetic Sampling*

Analysis will be performed to characterize EDI200 PK after the doses designated as dose #1 and #5. Blood samples (0.25 ml) for determination of EDI200 in plasma will be taken into collection tubes without additives on the days and times indicated. The model used to determine frequency of pharmacokinetic sampling incorporates a sparse sampling approach in order to reduce the number of blood samples required for each subject. Note that additional PK samples are scheduled for age 2 and 6 months to assess study drug persistence at low levels as was reported for XLHED adults.

PK samples will be drawn at approximately the following time points pre-dose (defined as prior to the start of infusion) and post-dose (defined as after infusion is completed):

	Pre-Dose	Post-Dose							
		15 (±5) min	3 (±.5) hrs	8 (±1) hrs	18 (±2) hrs	24(±2) hrs	48 (±4) hrs	168(±8) hrs	Age 2 months (±1 wk) & 6 months (±2 wks)
D0 (dose 1)	X	X	X	X		X	X		
D14 (dose 5)	X	X	X		X		X	X	X

Immediately upon sampling, the sample will be identified with a label bearing details of the study number, subject number, sampling time point, and a sample type. The sample will be separated by centrifugation at rotation 1500xg, 4°C for 10 minutes. Two 50 ul aliquots of serum will be transferred to polypropylene tubes labeled identically to the original blood sample and stored at approximately -70°C pending analysis. The time at which samples are taken, received into the separating room and placed in the freezer will be recorded in the study documentation.

4.5.3 *Immunogenicity Sampling*

Blood samples (~0.25 mL per sample) for immunogenicity sampling will be taken into serum separator tubes on the days indicated.

Immediately upon sampling, the sample will be identified with a label bearing details of the study number, subject number, sampling time point, and a sample type. The sample will be separated by centrifugation. Two equal aliquots of serum will be transferred to polypropylene tubes labeled identically to the original blood sample and stored at approximately -70°C pending analysis. The calendar date and 24-hour clock time at which samples are taken, centrifuged and placed in the freezer will be recorded in the study documentation.

4.5.4 *Total of Blood Volume*

The approximate number of safety laboratory evaluations and the approximate volume of blood that will be collected per subject throughout the study are as follows:

All Subjects	Genetic Testing (5 ml)*	Safety Labs (1.5 ml)	Immunogenicity (0.25 ml)	PK (0.25 ml)	Total Blood Volume (ml)	ml/kg (3.5 kg neonate)
Screening	0	0	0	0	0.00	
Baseline	1 x 5 = 5.0	1 x 1.5 = 1.5	1 x 0.25 = 0.25	0	6.75	1.93
Week 1	0	1 x 1.5 = 1.5	0	6 x 0.25 = 1.50	3.00	0.86
Week 2	0	0	0	0	0	0
Week 3	0	1 x 1.5 = 1.5	1 x 0.25 = 0.25	5 x 0.25 = 1.25	3.00	0.86
Week 4	0	1 x 1.5 = 1.5	0	1 x 0.25 = 0.25	1.75	0.50
Months 2,4,6	0	2 x 1.5 = 3.0	2 x 0.25 = 0.50	2 x 0.25 = 0.50	4.00	
Total	1 x 5 = 5.0	6 x 1.5 = 9.0	4 x 0.25 = 1.0	13 x 0.25 = 3.25	18.25	

* For testing of the EDAR polymorphism in the case that DNA is not available from prior genotyping

4.6 Safety Evaluations

The safety evaluations will consist of adverse events, concomitant medications, vital signs, weight, physical exam findings, and safety laboratory values. Adverse events will be recorded starting when the treatment Informed Consent document (ICF2) is signed and continuing until all study assessments are completed (including Month 6 follow-up evaluations for all AEs, and Month 6 + 28 days for SAEs). Information on the definition, characteristics, and reporting requirements are provided below.

4.6.1 *Adverse Events*

4.6.1.1 Definition

An adverse event (AE) is any reaction, side effect, or other untoward event (signs, symptoms, or changes in laboratory data) associated with participation in this study, whether or not the event is considered related to the study or any of the procedures being conducted. All AEs occurring after signing the informed consent document will be recorded. AEs will be ascertained on the basis of volunteered symptoms and clinical observation. AEs will be

recorded during the study on the appropriate CRF page. All AEs considered to be related to study procedures, and all serious adverse events (SAEs; see Section 4.5.2) will be followed until resolved or until a stable status has been achieved. SAEs will be recorded up to 28 days following the Day 168 visit.

4.6.1.2 Reporting Adverse Events

Any adverse event (AE, a clinical sign, symptom, or disease) temporally associated with this study, whether or not considered related to study drug, shall be documented on the case report form (CRF). All AEs reported by the subject or observed by the PI will be individually listed. The signs and symptoms, the date of onset, duration, relationship to study drug, action taken, and follow-up procedures will be reported.

4.6.1.3 Relationship

The relationship between an AE and the administration of study drug or the procedures employed in this study will be determined by the PI on the basis of his or her clinical judgment and the following definitions:

Definitely Related: Follows a reasonable temporal sequence from administration of study drug; follows a known response pattern to the study procedure; and, when appropriate to the protocol, is confirmed by improvement after stopping the study procedure (positive re-challenge) and by reappearance of the reaction after repeat exposure (positive re-challenge); and cannot be reasonably explained by known characteristics of the participant's clinical state or by other therapies.

Probably Related: Follows a reasonable temporal sequence from administration of study drug; follows a known response pattern to the study procedure; and, when appropriate to the protocol, is confirmed by improvement after de-challenge; and cannot be reasonably explained by the known characteristics of the participant's clinical state or by other therapies.

Possibly Related: Follows a reasonable temporal sequence from administration of study drug and follows a known response pattern to the study procedure but could have been produced by the participant's clinical state or by other therapies.

Unlikely Related: The reaction has little or no temporal sequence from administration of the study drug, and/or a more likely alternative etiology exists.

Not Related: Sufficient information exists to indicate that the etiology is unrelated to administration of study drug in this study. Two or more of the following variables apply:

- The AE does not follow a reasonable temporal sequence with occurrence of administration of study drug;

- The AE is readily explained by the participant's clinical state or other therapies.

4.6.1.4 Severity

The intensity of an AE, as determined by the PI, will be assessed and graded utilizing a 5-point scale according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v4.0). It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under section 4.6.2. If a subject experiences the same AE with more than one level of intensity, the highest level of intensity should be recorded on the CRF. The severity grading will be reported in the eCRF as follows:

Grade 1 = **Mild;** asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 = **Moderate**; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
Grade 3 = **Severe** or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
Grade 4 = **Life-threatening** consequences; urgent intervention indicated.
Grade 5 = **Death** related to AE.

4.6.1.5 Outcome

The outcome of an AE will be assessed as follows:

- Resolved
- Unresolved
- Resolved with sequelae
- Death
- Unknown

4.6.2 *Serious Adverse Event*

4.6.2.1 Serious Adverse Event Definition

An SAE is any AE that results in any of the following outcomes:

- Death
- A life threatening AE
  - The term "life-threatening" means that the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe
- An inpatient hospitalization or prolongation of existing hospitalization (24 hours or more)

- A persistent disability/incapacity, or a
- A congenital anomaly/birth defect
- Important medical event

An important medical event may not result in death, be life threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

4.6.2.2 Serious Adverse Event Reporting

The PI will report all SAEs to the Sponsor in a timely fashion, within 24 hours of awareness, by completing and faxing the SAE Report Form to CTI Safety as per directions described in the Study Reference Manual. The reporting PI is obligated to provide their initial assessment of the relationship between study drug and the occurrence of each SAE. Determination of expectedness and the reporting of the SAEs to relevant regulatory authorities will be determined by the Sponsor. The reporting PI is responsible for reporting all SAEs to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) as required by the appropriate regulations.

Based on the investigator's assessment of causality of the adverse event and discussions with the medical monitor, a decision will be made by the sponsor concerning the need for further action with respect to the future conduct of this trial. The primary consideration governing further action is whether new findings affect the safety of other subjects participating in the clinical study. If the discovery of a new adverse event related to study drug raises concerns over the safety of its continued administration to subjects, the sponsor or designee will take immediate steps to notify the Data Safety Monitoring Board (DSMB), the regulatory authorities and all the investigators participating in clinical studies of the study drug.

The Sponsor will notify the relevant regulatory authorities according to Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) regulations. The reporting PI will notify the Sponsor through the following contact:

Name:	CTI Global Drug Safety & Pharmacovigilance
Address:	10123 Alliance Road Cincinnati, OH 45242
Telephone:	1-877-755-0742
Fax:	1-866-215-5862
E-mail:	CTISafety@ctifacts.com

Additional SAE follow-up information, if required, should all be faxed to CTI Safety within 24 hours of receipt. The follow-up information should be documented on the original SAE Report Form following Good Documentation Practices and faxed with any additional relevant source

documentation. Additionally, the AE eCRF should be updated accordingly to match the SAE Report form.

SAE source documentation requested may include; discharge summary, diagnostic test results, consultation reports, relevant specimen cultures, diagnostics, or laboratory values. The investigator must ensure that all source documentation maintains each subject's anonymity. The site and subject number must be documented on every page, the subject's name replaced by the subject's study number, and all other protected health information should be redacted (e.g. social security number, medical record number, room number, etc.).

Compliance with the requirements for expedited reporting is essential. The sponsor or the sponsor's designee is responsible for informing the regulatory authorities as well as all other participating investigators of the following events:

- Any event associated with the use of the study drug, that is both serious and unexpected (SUSAR), or
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.

The sponsor or designee will expedite the reporting of all SUSARs to the appropriate regulatory authorities and the Institutional Review Board/Independent Ethics committee (IRB/IEC). The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse event (AE). For fatal or life threatening cases, the term will be a maximum of 7 calendar days for a preliminary report with another 8 calendar days for completion of the report. The sponsor or designee will also inform all investigators of such events.

The sponsor or designee will provide expedited reports of the following SUSARs to the IRB/IEC:

- SUSARs that have arisen in the clinical trial that were assessed by the EC
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that were assessed by the EC.

4.7 Concomitant Medication

There are no concomitant medications that are excluded from this study. There are no concomitant medications known to interact with EDI200.

4.8 Data Safety Monitoring Board (DSMB)

An independent DSMB will be established to monitor the safety of treated subjects. A European member has been added to the same DSMB in place for the Phase 1 adult safety

study (ECP-004) to monitor this neonate trial. All safety-related laboratory values will be available to the DSMB in real time. At the scheduled DSMB review meetings, detailed safety reviews will be provided to the DSMB including; adverse events, concomitant medications, infusion/injection site reactions, physical examination, weights and vital signs, and all PK and safety laboratory values. Scheduled DSMB meetings include the following:

- After dosing is completed in XLHED neonate cohort 1, the DSMB will meet and review safety and PK data from all cohort 1 subjects prior to initiation of dosing in XLHED neonate cohort 2. The timeframe for this review is approximately three weeks following dosing of the last cohort 1 subject. The cohort 1 PK data review is intended to confirm that the exposure levels in the cohort as a whole and for each subject were within the limits associated with safe study drug administration in the preclinical GLP toxicology studies, and that the expected exposure with dose escalation in cohort 2 will remain in the range that was safe and well tolerated. Additionally, the DSMB will review safety and PK data obtained from adult cohort 2 (NCT01564225, www.clinicaltrials.gov) dosed at the same 10 mg/kg/dose as is proposed for neonate cohort 2.
- At the end of the Study, DSMB will review and summarize all study safety data. DSMB summaries will be provided in a timely fashion to the Sponsor.

Unscheduled DSMB reviews will take place as outlined in Section 3.3.4-3.3.7 for single or accumulated adverse events. Additional safety-related evaluations of one or more subjects may be requested by the DSMB based on findings through the 6-month, end-of-study visit.

5 SCHEDULE OF STUDY ASSESSMENTS

5.1 Screening – End of first trimester through DOL #12

- Medical history related to XLHED in the family and for pregnancy, labor and delivery
- Verbal consent from both parents (if reasonably available) to provide documentation of genetic testing results to the study site by a secure and confidential method including the option for electronic transmission
- Inclusion/Exclusion criteria will be confirmed for parents and fetus/neonate

**A screening call may be conducted to assess eligibility for study participation, inclusion/ exclusion criteria, and availability of EDA genetic test results. If prior genotyping is not available, either cord blood or a neonatal blood sample may be sent to an accredited laboratory for testing.*

5.2 Baseline – DOL #2 through DOL #14

- Transport Informed Consent from both parents (if reasonably available) if neonatal transport to the study site is to be provided as part of the study
- Treatment Informed Consent from both parents (if reasonably available) for study procedures and study drug administration
- Confirmation of inclusion/exclusion criteria
- Updated medical history
- Full physical examination
- Blood draws for safety laboratories, EDAR gene V370A polymorphism testing, PK and immunogenicity
- Bioactivity assessments
    - Growth and development
    - Dental imaging
    - Digital facial photograph
    - Sweat duct density
    - Sweat rate
    - Dry eye assessment
    - Thermoregulation
    - Skin biopsy sample for molecular profiling
- Adverse Events & Concomitant Medications

5.3 Treatment

Day 0

- Brief physical exam (prior to dosing)
- Study drug administration (dose 1)
- Vital sign monitoring during and for 24 hours following study drug infusion
- Blood draw for PK analysis at the following timepoints:
    - Post-end of infusion timepoints: 15 min, 3 and 8 hours
- Adverse Events & Concomitant Medications

Day 1

- Brief physical exam
- Blood draw for safety laboratory evaluations
- Blood draw for PK analysis at the following timepoints:
    - 24 hours post dose 1
- Skin biopsy 24 hours post dose 1
- Adverse Events & Concomitant Medications

Day 2

- Blood draw for PK analysis at the following timepoints:
    - 48 hours post dose 1
- Adverse Events & Concomitant Medications

Day 4

- Brief physical exam (prior to dosing)
- Study drug administration (dose 2)
- Vital sign monitoring during and for 24 hours following study drug infusion
- Adverse Events & Concomitant Medications

Day 7

- Brief physical exam (prior to dosing)
- Study drug administration (dose 3)
- Vital sign monitoring during and for 24 hours following study drug infusion
- Adverse Events & Concomitant Medications

Day 11

- Brief physical exam (prior to dosing)
- Study drug administration (dose 4)
- Vital sign monitoring during and for 24 hours following study drug infusion
- Adverse Events & Concomitant Medications

Day 14

- Brief physical exam (prior to dosing)
- Study drug administration (dose 5)
- Vital sign monitoring during and for 24 hours following study drug infusion
- Blood draws for PK analysis at the following timepoints:
    - Pre-dose and the following post-end of infusion timepoints: 15 minutes, 3 and 18 hours
- Adverse Events & Concomitant Medications

Day 15

- Brief physical exam
- Skin biopsy for molecular profiling (24 hours after study drug administration)
- Adverse Events & Concomitant Medications

Day 16

- Blood draw for PK analysis at the following timepoints:
    - 48 hours post dose 5
- Blood draw for safety laboratory evaluations
- Blood draw for immunogenicity testing
- Adverse Events & Concomitant Medications

Day 21

- Full physical exam
- Blood draw for safety laboratory evaluations
- Blood draw for PK analysis at the following timepoints:
    - 168 hours post dose 5
- Thermoregulation assessment
- Adverse Events & Concomitant Medications

**If any visits are adjusted during the baseline and/or treatment portions of the study (if a subject is seen or dosed earlier or later than what is described in the protocol) then all subsequent visits (if applicable) should be adjusted accordingly.*

5.4 Post-Treatment

Follow-Up Visit 1 – Month of Life 2 (±1 week)

- Full physical exam
- Blood draw for safety laboratory evaluations
- Blood draw for immunogenicity testing
- Blood draw for PK
- PD/efficacy assessments
    - Growth and development

  - Sweat duct density
  - Sweat rate
  - Dry eye assessments
- Adverse Events & Concomitant Medications

Follow-Up Visit 2 – Month of Life 4 (±1 week)

- Full physical exam
- PD/efficacy assessments
  - Growth and development
- Adverse Events & Concomitant Medications

End-of-Study Visit – Month of Life 6 (±2 weeks)

- Full physical exam
- Blood draw for safety laboratory evaluations
- Blood draw for immunogenicity testing
- Blood draw for PK
- PD assessments
  - Growth and development
  - Digital facial photographs
  - Sweat duct density
  - Sweat rate
  - Dry eye assessments
- Adverse Events & Concomitant Medications

5.5 Unscheduled Visits

The Sponsor or DSMB may request unscheduled visits either during the subject's participation in the Study or after his completion. The unscheduled visits may include additional safety-related evaluations (including blood sampling) based on findings through the 6-month, end-of-study visit.

6 STATISTICAL METHODS

6.1 Sample Size

The sample size is based on clinical and practical considerations for a Phase 2 study in an ultra-rare genetic disorder with enrollment limited to newborns. It is considered to be appropriate to meet the objectives of the study while minimizing the exposure of volunteers. Each cohort is anticipated to enroll approximately 3-7 XLHED-affected neonates. No more than 10 subjects total will be enrolled.

6.2 Analysis Datasets

The safety analysis set will consist of all subjects who receive at least one dose of study medication. The PK analysis set will consist of those subjects who receive at least one dose of study medication and have sufficient concentration data to obtain a plasma concentration by time profile. The PD/efficacy analysis set will consist of all subjects who receive at least one dose of study medication and complete the follow-up assessments through at least month 2. No missing data will be replaced by values carried forward.

6.3 Primary and Pharmacodynamic/Efficacy Assessments

The safety assessment variables are AEs, concomitant medications, vital signs, weight, physical examination findings, hematology, clinical chemistry, and urinalysis laboratory test results.

The PK assessment variables will be the following derived PK parameters for EDI200:

- C_{max}, T_{max}, $AUC_{0\text{-}tau}$
- Other PK parameters including but not limited to clearance rate may also be examined.

The medical history and clinical evaluations for the sibling sub-study will be tabulated and intra-familial comparisons will be made with data obtained from the neonate subjects receiving study drug.

The following pharmacodynamic/efficacy outcomes will be monitored in all subjects receiving study drug:

- Growth and development
- Dentition (follow-up radiographs in extension study)
- Craniofacial development by digital photography
- Sweat duct density
- Sweat rate
- Dry eye signs and symptoms
- Thermoregulation
- Molecular expression profile of skin biopsy tissue

6.4 Pharmacodynamic/Efficacy Variables (not including sibling sub-study)

Growth and Development
Testing to be performed at Baseline, Months of Life 2, 4, 6:

- Weight, length, head circumference plotted on standardized growth curves for males
- Developmental assessments

Dental Imaging:
Testing to be performed at Baseline:

- Lateral jaw film

Craniofacial Development
Testing to be performed at Baseline, Month of Life 6

- Digital facial photographs

Sweat Duct Density
Testing to be performed at Baseline, Months of Life 2 and 6:

- Sweat ducts per 36 mm^2 on confocal microscopy image

Sweat Rate:
Testing to be performed at Baseline, Months of Life 2 and 6:

- Volume of induced sweat collected over 30 minutes following pilocarpine iontophoresis

Dry Eye Assessments:
Testing to be performed at Baseline, Months of Life 2 and 6:

- Examination for signs of infection and/or irritation, as well as tear film break-up time

Thermoregulation
Testing to be performed at Baseline, TD21:

- Clinical and vital sign response to isolette temperature range

Skin Biopsy for Molecular Expression Profile:
Testing to be performed at Baseline, TD1 (approximately 24 hours after 1st dose) and TD15 (approximately 24 hours after last dose):

- Analysis of gene expression on skin biopsy samples

6.5 Analysis of Safety and Pharmacokinetic Variables

Safety variables will be tabulated and presented for all subjects receiving one or more doses of EDI200. Change from Baseline over time will be presented by cohort for continuous variables including laboratory values and vital signs using descriptive statistics with n, mean, standard

deviation, minimum, median and maximum as appropriate. Shift tables will be presented. Out-of-range values will be flagged in the data listings and will also be presented separately.

AEs will be coded using the current MedDRA drug dictionary version. Only treatment emergent AEs will be included in the summary tables. The incidence of subjects reporting AEs will be summarized by system organ class, preferred term, severity and relationship to study drug.

The PK parameters of EDI200 will be listed and summarized by dosing cohort. Mean and individual plasma concentration-time curves will be presented on both linear and semi-logarithmic scales. The derivation of the PK variables from the EDI200 plasma concentrations will be determined using WinNonlin Professional v5.2, or higher. The PK parameters of EDI200 will be listed and summarized.

6.6 Statistical Methods

Individual subject values for EDA genotype and all endpoints, both at Baseline and across time, will be provided. Demographics for the entire study dataset will be presented using descriptive statistics. Table summaries of Baseline values for all endpoints will be provided for the following groups: all subjects and each dosing cohort. Descriptive statistics will be provided across time for each cohort with n, mean, standard deviation, minimum, median and maximum as appropriate.

6.7 Data Management

As outlined in section 7.5 the Sponsor or designee will forward questions regarding missing data or discrepancies to the PI.

The original terms used in the case report forms by the PI to identify adverse events will be coded according to the MedDRA dictionary. The percentage of subjects with adverse events will be tabulated overall and by the MedDRA body system and preferred term.

7 STUDY ADMINISTRATION

7.1 Protocol Modifications

Neither the PI nor Sponsor will modify this protocol without obtaining the concurrence of the other. All protocol amendments must be issued by the Sponsor, signed and dated by the PI, and should not be implemented without prior IRB/IEC approval, except where necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study (e.g., typographical errors, inconsistencies).

In situations requiring a departure from the protocol, the PI or other physician in attendance will discuss with the appropriate Sponsor representative. This contact will be made before implementing any departure from protocol. In all cases, contact with the Sponsor will be made as soon as possible in order to discuss the situation and agree on an appropriate course of action. Any departure from the protocol and the circumstances requiring it will be documented.

7.2 Monitoring

The Sponsor or their designee (hereby referred to as “Monitor”) will monitor all aspects of the study as required by GCP and any existing standard operating procedures for compliance with applicable regulations. These individuals will have access to all records necessary to ensure integrity of the data and will review progress of the study with the PI.

The monitor will compare the data entered into the CRF’s with any source documents. The nature and location of any source documents will be identified in advance. This will ensure that all sources of original data required to complete the CRF are known to the Sponsor and investigational staff; and are accessible for verification by the Monitor. If electronic records are maintained, the method of verification must be discussed with the investigational staff. At a minimum, source documentation must be available to substantiate subject identification, eligibility and participation, proper informed consent procedures, adherence to protocol procedures, record of safety parameters, adequate reporting and follow-up of adverse events, completion and reason of withdrawal/ termination. Specific items required as source documents will be reviewed with the PI before the study. The author of an entry in the source documents will be identifiable.

If any data are recorded directly into the CRF, at a minimum there should be an entry in the source document that each of the assessments was done, and by whom and the date it was done. The author of an entry in the source documents must be identifiable. The CRF data will be entered into an appropriate data storage system and verified for accuracy.

Direct access to source documentation must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. Findings from this review

of CRF's and source documents will be discussed with the investigational staff. The Sponsor expects that, during monitoring visit(s), the relevant investigational staff will be available, the source documentation will be available, and a suitable environment will be provided for review of study-related documents. The monitor will provide feedback on the study conduct to the PI.

The investigator will permit trial-related monitoring, audits, audits, IRB/IEC review, and regulatory inspection(s), and providing direct access to source data/documents.

7.3 Ethic Aspects

7.3.1 PI Responsibilities

The PI is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines, Good Clinical Practice (GCP), and applicable regulatory requirements.

GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well being of study subjects are protected, consistent with the principles that have originated in the Declaration of Helsinki and that the clinical study data are credible.

7.3.2 Institutional Review Board/Independent Ethics Committee

The PI will provide the Institutional Review Board/Independent Ethics committee (IRB/IEC) with all requisite material, including a copy of the protocol, informed consent and all subject materials. The study will not be initiated until the IRB/IEC provides written approval of the protocol and the informed consent and the PI has obtained documents approved by the IRB/IEC. Any reports requested on the progress of this study by the PI will be made to the IRB/IEC and the Sponsor.

7.3.3 Informed Consent

A properly executed, written informed consent in compliance with national and local regulations and GCP guidelines will be obtained from each subject prior to entering the study or performing any study-related procedure.

The PI will submit a copy of the informed consent document to the IRB/EC for review and approval before research subjects are enrolled. The PI will provide a version of the signed informed consent to the subject and a signed version will be maintained in the subject's research record.

7.3.4 Confidentiality of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the safety, quality, and utility of the procedures performed during this study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

The Sponsor ensures that the personal data are:

- Processed fairly and lawfully
- Collected for specified, explicit, and legitimate purposes and not further processed in a way incompatible with these purposes
- Adequate, relevant, and not excessive in relation to said purposes
- Accurate and, where necessary, kept up to date

Explicit consent for the processing of personal data will be obtained from the participating subject before collection of data. Such consent should also address the transfer of the data to other entities and to other countries, if applicable.

The subject has the right to request through the PI access to his/her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps should be taken to respond to such request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel and designees whose responsibilities require access to personal data agree to keep the identity of study subjects confidential.

7.4 Subject Identification Register

The PI agrees to complete a subject identification register to permit easy identification of each subject during and after the study. The Monitor will review the document for completeness.

The subject identification register will be treated as confidential and will be filed by the PI in the Regulatory Binder. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by initials and assigned number only.

7.5 Case Report Form Completion

All of the clinical data will be captured via electronic data capture (EDC) using an approved and validated EDC system. The investigator site staff will enter and edit the data via a secure network, with secure access features (username, password and secure identification – an electronic password system). A complete electronic audit trail will be maintained.

The investigator will approve the data using an electronic signature, and this approval is used to confirm the accuracy of the data recorded (CFR 21, Part. 11, 2011).

Electronic CRF's (eCRF) will be used for all patients. The investigator's data will be accessible from the investigator's site throughout the trial. The eCRFs must be kept current to reflect patient status at each phase during the course of the trial. The patients must not be identified on the eCRF by name. The appropriate coded identification (i.e. Patient Number) must be used. The investigator must make a separate confidential record of these details (subject identification record) to permit identification of all patients enrolled in a clinical trial in case follow-up is required.

Copies of the eCRF together with all data changes made will be supplied to the investigator at the end of the trial. The investigator will be responsible for retaining all records pertaining to the trial as specified in the appropriate contract.

7.6 Data Quality Assurance

Steps to be taken to assure the accuracy and reliability of data include the selection of a qualified PI, review of protocol procedures with the PI and associated personnel before the study, and a monitoring visit(s) by the Sponsor. Instruction for completion of CRFs will be provided and reviewed with study personnel before the start of the study. The Monitor will review CRFs for accuracy and completeness during the conference and/or during a monitoring visit(s). Any discrepancies will be resolved with the PI or designee, as appropriate. The data will be entered into an appropriate data storage system and verified for accuracy.

7.7 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

APPENDIX 1 – AUTOMATIC PHENOTYPE IDENTIFICATION OF XLHED PATIENTS

FINAL REPORT

Provided as a separate document.

APPENDIX 2 – THE NATIONAL CANCER INSTITUTE (NCI) COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS V4.0 (CTCAE)

VERSION 4.0

US DEPARTMENT OF HEALTH AND HUMAN SERVICES- NATIONAL INSTITUTES OF HEALTH-NATIONAL CANCER INSTITUTE

Provided as a separate document.

APPENDIX 3 – MEDICAL QUESTIONNAIRE FOR MOTHERS AND XLHED-AFFECTED NEONATES

Medical Questionnaire for Mothers and XLHED-Affected Neonates

Participant's Initials: ☐☐☐ **Can be left blank if choice of name is not yet finalized*

Today's Date: ☐☐/☐☐/☐☐☐☐

Date of birth: ☐☐/☐☐/☐☐☐☐

DD/MM/YYYY

Has the mother been diagnosed with HED? ☐Yes ☐No

If yes, age at diagnosis: ☐0-5 years ☐6-17 years ☐≥18 years

Does the mother have any family members diagnosed with HED? ☐Yes ☐No

If yes, check all that apply:
☐Mother
☐Father
☐Sisters
☐Brothers
☐Aunts
☐Uncles
☐Other

If other, specify:

Has the mother or any family member(s) had genetic testing for HED? ☐Yes ☐No

**Every attempt should be made to obtain a copy of the genetic test results. The results must be provided to the study site and will also be provided to the lab conducting your baby's genetic testing in order to expedite the testing process.*

Mother's age at delivery: ☐☐

What number pregnancy is/was this child for the mother? ☐☐

Is the mother currently pregnant? ☐Yes ☐No

Thinking of *all* of the mother's pregnancies to date, including this one, how many resulted in each of the following:

	Number
Miscarriage in the first trimester (up to 14th week of pregnancy)	☐☐
Miscarriage later in pregnancy	☐☐
Stillbirth	☐☐
Preterm birth (prior to 37 weeks)	☐☐
Full term birth (37 weeks or more)	☐☐

Did the mother have any of the following complication during ***this child's*** (the study subject) pregnancy? ☐Yes ☐No

If yes, please list treatment.

Diabetes: _____
High blood pressure: _____
Infections, fevers and illnesses: _____
Other problems/complications: _____

Medications used during pregnancy: _____
_____

Are any of these medications investigational? ☐ Yes ☐ No

Did the mother have any of the following?
☐ Ultrasound
☐ 1st trimester screen/triple/quad screen
☐ Amniocentesis or CVS

Were any results from this testing abnormal? ☐ Yes ☐ No

If yes, please explain:
_____
_____

Check here ☐ if your child is not born yet and do NOT complete the rest of this form.

The child was born:
☐ Full-term
☐ Prematurely (weeks premature: ☐☐)

If premature, please list the reason:
_____

The child was born: ☐ Vaginally ☐ By C-section
If by C-section, why: _____

Birth Hospital: _____

Birth location:

Country: _____
City: _____
State (if applicable): _____

Birth weight: ☐☐.☐☐ kg
Birth Length: ☐☐☐ . ☐☐ cm
Birth head circumference: ☐☐☐ . ☐☐ cm

Did your child have any problems after delivery or require admission to the Neonatal Intensive Care Unit (NICU)? ☐ Yes ☐ No

If yes, please explain:

_____

_____

Did he/she pass the:
Newborn metabolic screen: ☐ Yes ☐ No ☐ Unsure
Newborn hearing screen: ☐ Yes ☐ No ☐ Unsure

How many days old was child when he/she went home from the hospital? ☐☐

Did the child have any other problems in the first few days of life? ☐ Yes ☐ No
If yes, please explain: _____

_____

APPENDIX 4 – MEDICAL QUESTIONNAIRE FOR MALE SIBLINGS OF STUDY SUBJECTS

Medical Questionnaire for Male Siblings of Study Subjects

*One questionnaire to be completed by each male sibling

Participant's Initials: ☐☐☐

Participant's ID #: ☐☐☐
*To be completed by study personnel

Gender: ☐Male

Today's Date: ☐☐/☐☐/☐☐☐☐

Date of birth: ☐☐/☐☐/☐☐☐☐
DD/MM/YYYY

Are you currently experiencing any major medical problems that would prevent you from participating in this study? ☐Yes ☐No

Do you have a known hypersensitivity to pilocarpine or pilocarpine-like muscarinic agonists (Examples: Urecholine, Salagen, Pilocar, and Provocholine)? ☐Yes ☐No

Do you have a pacemaker? ☐Yes ☐No

Have you been diagnosed with HED? ☐Yes ☐No

If yes, age at diagnosis: ☐0-5 years ☐6-17 years ☐≥18 years

Do you have any family members diagnosed with HED? ☐Yes ☐No

If yes, check all that apply:
☐Mother
☐Father
☐Sisters
☐Brothers
☐Aunts
☐Uncles
☐Other

If other, specify:

Have you or any family member(s) had genetic testing for HED? ☐Yes ☐No

Do you know the genetic test results? ☐Yes ☐No

Have you ever been referred to any of the following types of physicians?

Dermatologist	☐Yes	☐No
Pediatric dermatologist	☐Yes	☐No
Geneticist	☐Yes	☐No
Genetic counselor	☐Yes	☐No
Dentist	☐Yes	☐No
Pediatric dentist	☐Yes	☐No

Do you have decreased sweating?	☐Yes ☐No
Do you sweat on certain parts of your body?	☐Yes ☐No
If so, from what body part(s) do you sweat and at what age did you notice you started sweating in that area?	
Body Part: ____________ Age you noticed:	☐0-5 yrs ☐11-17 yrs ☐6-10 yrs ☐≥18 yrs
Body Part: ____________ Age you noticed:	☐0-5 yrs ☐11-17 yrs ☐6-10 yrs ☐≥18 yrs
Body Part: ____________ Age you noticed:	☐0-5 yrs ☐11-17 yrs ☐6-10 yrs ☐≥18 yrs
Body Part: ____________ Age you noticed:	☐0-5 yrs ☐11-17 yrs ☐6-10 yrs ☐≥18 yrs
Body Part: ____________ Age you noticed:	☐0-5 yrs ☐11-17 yrs ☐6-10 yrs ☐≥18 yrs
Body Part: ____________ Age you noticed:	☐0-5 yrs ☐11-17 yrs ☐6-10 yrs ☐≥18 yrs
Do you have unexplained fevers?	☐Yes ☐No
Did you ever suffer from seizures associated with fever?	☐Yes ☐No
Do you suffer from heat intolerance?	☐Yes ☐No
Is your exercising limited by heat intolerance?	☐Yes ☐No

Does your decreased sweating/heat intolerance affect your: **Check all that apply*	☐Daily life ☐Choice of occupation ☐Involvement in indoor sports ☐Involvement in outdoor sports ☐Decision to live in cooler climate ☐Choice of vacation destinations ☐Ability to travel

Have you experienced hair or eyebrow thinning or scalp hair loss?	☐Yes ☐No
If yes, what age were you when you noticed the loss of hair?	☐0-5 yrs ☐6-10 yrs ☐11-17 yrs ☐≥18 yrs
How often do you get your hair cut?	☐Daily ☐Weekly ☐ Monthly ☐Yearly
Do you get haircuts less often than unaffected siblings/ classmates?	☐ Yes ☐ No
Have you ever tried a topical treatment to reduce hair thinning?	☐Yes ☐No

Do you have problems with your teeth (no teeth, missing or misshapen teeth)?			☐Yes ☐No
If yes, describe age of treatment with dentures and/or implants if applicable (check all that apply):		Dentures	Implants
	1-5 years	☐	☐
	6-10 years	☐	☐
	11-17 years	☐	☐
	≥18 years	☐	☐
To the best of your knowledge how many baby teeth did you develop?			☐☐
To the best of your knowledge how many adult teeth did you develop?			☐☐
Do you suffer from dry mouth?			☐Yes ☐No
Do you suffer from dry eyes?			☐Yes ☐No
Do you require eye drops on a regular basis?			☐Yes ☐No
Do you suffer from frequent eye infections?			☐Yes ☐No

Did you have chronic nasal drainage/blockage as a child?		☐Yes ☐No
Did you suffer from nosebleeds as a child?		☐Yes ☐No
If yes, at what age did you first notice them?	☐0-5 yrs ☐6-10 yrs	☐11-17 yrs ☐≥18 yrs
Do you still experience nosebleeds?		☐Yes ☐No
How many times per year do you have nosebleeds?	☐☐	
Did you have respiratory related problems as a child?		☐Yes ☐No
If yes, were you ever hospitalized for antibiotic therapy?		☐Yes ☐No
Do you suffer from sinus infections most years?		☐Yes ☐No
If so, at what age did these sinus infections start?	☐0-5 yrs ☐6-10 yrs	☐11-17 yrs ☐≥18 yrs
Do you suffer from asthma?		☐Yes ☐No
If so, do you require medication to manage your asthma?		☐Yes ☐No
Do you experience a hoarseness of your voice?		☐Yes ☐No
If yes, at what age did you first notice it?		☐Yes ☐No
Is the hoarseness worse during the cold months?		☐Yes ☐No

Do you have problems with dry skin?	☐Yes ☐No
Have you ever had a diagnosis of eczema or atopic dermatitis?	☐Yes ☐No
If yes, have you tried prescription medications?	☐Yes ☐No

If yes, list medications:

Do you have a family history of eczema (other than XLHED males)? ☐Yes ☐No

Hypohidrosis Severity 5-Point Likert Scale

1	2	3	4	5
Sweat as much as people without ED	Sweat a little less than people without ED (no problems in hot weather)	Some problems in sweating (sometimes have problems in hot weather)	A little sweating (I have problems in hot weather	No sweating at all (I have problems in hot weather)

Alopecia (hair loss or thinning) Severity 5-Point Likert Scale

1	2	3	4	5
Normal hair	Mild (<25%) hair loss	Moderate (25-75%) hair loss	Severe (>75%) hair loss	No hair

APPENDIX 5 – OCULAR SURFACE DISEASE INDEX© (OSDI©)

Provided as a separate document.

REFERENCES

Black, MM, Matula K. 2000. *Essentials of Bayley Scales of Infant Development-II Assessment*. New York, J Wiley & Sons, Inc.

Blüschke G, Nusken KD, Schneider H. 2010. Prevalence and prevention of severe complications of hypohidrotic ectodermal dysplasia in infancy. *Am J Med Gen A*. 86: 397-9.

Casal M, Lewis J, Mauldin E, Tardivel A, Ingold K, Favre M, Paradies F, Demotz S, Gaide O, Schneider P. 2007. Significant Correction of Disease after Postnatal Administration of Recombinant Ectodysplasin A in Canine X-Linked Ectodermal Dysplasia. *Am J Hum Genet*. 81: 1050-1056.

Chawla, D, Agarwal R, Deorari A, Paul, V. 2008. Fluid and electrolyte management in term and preterm neonates. NICU Protocol. Division of Neonatology, Department of Pediatrics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi.

Clarke A, Sarfarazi M, Thomas NS, Roberts K, Harper PS. 1987. X-linked hypohidrotic ectodermal dysplasia: DNA probe linkage analysis and gene localization. *Hum Genet.* 75(4): 378-80.

Cloherty JP, Eichenwald EC, Stark AR. 2004. Manual of Neonatal Care (Fifth Ed). Philadelphia, PA: Lippincott, Williams & Wilkins.

Cluzeau C, Hadj-Rabia S, Bal E, Clauss F, Munnich A, Bodemer C, Headon D, Smahi A. 2012. The EDAR370A allele attenuates the severity of hypohidrotic ectodermal dysplasia caused by EDA gene mutation. *Br J Dermatol* 166:678-81.

Dietz J, Kaercher T, Schneider AT, Zimmerman T, Huttner K, Johnson R, Schneider H. 2013 Apr 4. Early respiratory and ocular involvement in X-linked hypohidrotic ectodermal dysplasia. *Eur J Pediatr* Epub ahead of print.

Ectodysplasin A (Fc:EDA1 aka EDI200) Replacement Therapy In A Canine Model Of Ectodermal Dysplasia: Pharmacological Assessment (NCD-200-11-005). Edimer Pharmaceuticals, Inc.

EDI200: A 3-Week Intraperitoneal/Intravenous Toxicity Study in Juvenile Dogs with a 2-Week Recovery Period (1800-010). Edimer Pharmaceuticals, Inc.

EDI200: A 3-Week Intraperitoneal Toxicity Study in Juvenile Mice with a 2-Week Recovery Period (1800-009). Edimer Pharmaceuticals, Inc.

"Electronic Records: Electronic Signatures." *Code of Federal Regulations* Title 21, Pt. 11, 2011 ed.

Gaide O, Schneider P. 2003. Permanent Correction of an Inherited Ectodermal Dysplasia with Recombinant EDA. *Nat Med*. 9: 614-618.

Haycock, G. B., Schwartz, G. J., & Wisotsky, D. H. 1978. Geometric method for measuring body surface area: a height-weight formula validated in infants, children, and adults. *J Pediatr*. 93(1), 62-6.

Hey E. 1975. Thermal neutrality. *British Med Bull*. *31*(1): 69-74.

Huttner K, Grange D, Klein O, Schneider H. 2012, February. Genotype/phenotype correlations in XLHED: Insights into the biology of ectodysplasin. Poster session presented at the 2012 Dermatogenetics Conference. Miami, Florida.

Itoh H, Uebori S, Asai M, Kashiwaya T, Atoh K, Makino I. 2003. Early Detection of Orthostatic Hypotension by Quantitative Sudomotor Axon Reflex Test (QSART) in Type 2 Diabetic Patients. *Internal Med*. 42: 560-564.

Low P, Caskey P, Tuck R, Fealey R, Dyck P. 1983. Quantitative Sudomotor Axon Reflex Test in Normal and Neuropathic Subjects. *Ann Neurol*. 14: 573-580.

Mastella G, Di Cesare G, Borruso A, Menin L, Zanolla L. 2000. Reliability of sweat testing by the Macroduct collection method combined with conductivity analysis in comparison with the classic Gibson and Cooke technique. *Acta Paediatrica. 89*(8): 933-7.

Mauldin E, Gaide O, Schneider P, Casal M. 2009. Neonatal Treatment with Recombinant Ectodysplasin Prevents Respiratory Disease in Dogs with X-Linked Ectodermal Dysplasia. *Am J Med Genet A.* 149A: 2045-2049.

Miller, R. 2003. Marginal Transfer of ReoPro™ (Abciximab) Compared with Immunoglobulin G (F105), Inulin and Water in the Perfused Human Placenta In Vitro. *Placenta*. *24*(7): 727-738.

Motil KJ, Fete TJ, Fraley JK, Schultz RJ, Foy TM, Ochs U, et al. 2005. Growth Characteristics Of Children With Ectodermal Dysplasia Syndromes. *Pediatrics*. 116(2): 229-34.

Ramaswami U, Wendt S, Pintos-Morell G, Parini R, Whybra C, Leon Leal J, Santus F, Beck M. 2007. Enzyme Replacement Therapy with Agalsidase Alfa in Children with Fabry Disease. *Acta Paediatr*. 96: 122-127.

Rutter N, Hull D. 1979. Response of term babies to a warm environment. *Arch Dis Child. 54*(3): 178-183.

Seeliger F, Drögemüller C, Tegtmeier P, Baumgärtner W, Distl O, & Leeb T. 2005. Ectodysplasin-1 deficiency in a German Holstein bull associated with loss of respiratory mucous glands and chronic rhinotracheitis. *J Comp Pathol*. 132(4): 346-9.

Sjörs G, Hammarlund K, Sedin, G. 1997. Thermal balance in term and preterm newborn infants nursed in an incubator equipped with a radiant heat source. *Acta Paediatrica. 86*(4): 403-9.

Stothers J K, Warner R M. 1984. Thermal balance and sleep state in the newborn. *Early Hum Dev*. *9*(4): 313-22.

Sulyok E, Jequier E, Prod'hom L. 1976. Relationship between body size, thermal balance and thermal insulation of term infants under various ambient conditions. *Biol Neonate*. *28*: 42-56.

Sweat Duct Imaging in Mother/Newborn Dyads (ECP-005). Clinical Study Report. Edimer Pharmaceuticals, Inc.

Swischuk, L. 2003. Imaging of the Newborn, Infant and Young Child (Fifth). Philadelphia, PA: Lippincott, Williams and Wilkins.

The Effect of Ectodysplasin A (Fc: EDA1) Replacement Therapy in a Canine Model of Ectodermal Dysplasia (NCD-22-11-004). Edimer Pharmaceuticals, Inc.

Ulm M R, Kratochwil A, Ulm B, Solar P, Aro G, Bernaschek, G. 1998. Three-dimensional ultrasound evaluation of fetal tooth germs. *Ultrasound Obst Gyn*. *12*(4): 240-3.

Zankl A, Addor M, Cousin P, Gaide A, Gudinchet F, Schorderet D. 2001. Fatal outcome in a female monozygotic twin with X-linked hypohidrotic ectodermal dysplasia (XLHED) due to a de novo t(X;9) translocation with probable disruption of the EDA gene. *Eur J Pediatr*. 160: 296-99.

Protocol Version 3.1 (UK Only)
28 Oct 2013

Clinical Protocol

A Phase 2 open-label, dose-escalation study to evaluate the safety, pharmacokinetics, immunogenicity and pharmacodynamics/efficacy of EDI200, an EDA-A1 replacement protein, administered to male infants with X-Linked Hypohidrotic Ectodermal Dysplasia (XLHED)

Protocol: ECP-002

Investigational Product: EDI200

Sponsor:

Edimer Pharmaceuticals, Inc.
55 Cambridge Parkway
Suite 102W
Cambridge MA 02142

IND Number: 109262
EudraCT Number: 2012-003561-17

Issue Date: 28OCT2013
Version: 3.1 (UK Only)

TABLE OF CONTENTS

PROTOCOL AMENDMENTS

Previous Versions
19FEB2013, original
02APR2013, version 2*
*Version 2 was issued prior to the enrollment of subjects and included only minor changes for clarification
12JUN2013, version 3

Amendment #/Date	Applicable Section	Original Text	New/Revised Text/Description	Rationale
3 12JUN2013	Cover Page, Synopsis	A Phase 2 open-label, dose-escalation study to evaluate the safety, pharmacokinetics and pharmacodynamics/efficacy of EDI200, an EDA-A1 replacement protein, administered to male infants with X-Linked Hypohidrotic Ectodermal Dysplasia (XLHED)	A Phase 2 open-label, dose-escalation study to evaluate the safety, pharmacokinetics, immunogenicity and pharmacodynamics/efficacy of EDI200, an EDA-A1 replacement protein, administered to male infants with X-Linked Hypohidrotic Ectodermal Dysplasia (XLHED)	Immunogenicity added to study title
3 12JUN2013	Executive Summary	See 02APR2013 protocol version 2	Several minor changes made to Executive Summary	Clarification
3 12JUN2013	Time and Events Schedule	Change made to biopsy and PK sample schedule	Biopsy removed from Month 6 visit, PK sample removed from Day 15 visit	Correction and clarification
3 12JUN2013	Time and Events Schedule	Change made to PK sample schedule	PK sample added to baseline and month 6	Modification of PK sample schedule (similar minor changes made throughout protocol)
3 12JUN2013	Time and Events Schedule	Change made to safety labs and immunogenicity sample schedule	Safety labs and immunogenicity sample moved from day 15 to day 16	Modification of safety labs and immunogenicity sample schedule (similar minor changes made throughout protocol)
3 12JUN2013	Time and Events Schedule	A full physical exam will be conducted at baseline, treatment days 7 and 14 and at the months 2, 4 and 6 follow-up visits. The full physical exam will include weight, height, head circumference and vital signs. A brief physical exam will be conducted at treatment days 0, 1, 4, 11,	A full physical examination will be conducted at baseline, day 21, months 2, 4, and 6. With the full physical examination will be the following quantitative assessments; weight, height, head circumference and vital signs (temperature, blood pressure, heart rate and respiratory rate). A brief	Clarification on components of brief and full physical exam

		15 and 21. The brief physical exam will include vital signs. On dosing days vital signs will also be collected every 4 hours following the end of the infusion for 24 hours.	physical examination will be conducted at treatment days 0, 1, 4, 7, 11, 14 and 15. The brief physical examination will include overall appearance (normal or abnormal and if abnormal why), skin appearance, cardiovascular, pulmonary and abdominal evaluation. With the brief physical examination will be weight and a set of vital signs (temperature, blood pressure, heart rate and respiratory rate). On dosing days vital signs will also be collected pre- and post dosing as described in section 3.3.8.	
3 12JUN2013	Time and Events Schedule, 4.5.2	New text added	Time windows added for acceptable sampling	Provision for obtaining samples outside of specified time points
3 12JUN2013	Time and Events Schedule	Subjects may provide dental X-rays from an outside source. No dental radiographs will be obtained at the study site.	No dental radiographs will be taken as part of this sibling sub-study. Subjects will be asked to provide copies of recent dental X-rays from an outside source.	Clarification that no dental radiographs are done as part of the sibling sub-study (similar minor changes made throughout protocol)
3 12JUN2013	Time and Events Schedule	See 02APR2013, protocol version 2	Several minor changes made to Time and Events Schedule	Clarification
3 12JUN2013	1.1	See 02APR2013, protocol version 2	Several minor changes made	Clarification
3 12JUN2013	3	See 02APR2013, protocol version 2	Several minor changes made	Clarification
3 12JUN2013	3.1.5	The schedule of events for the In-Clinical portion of the study is presented in the Time and Events Table. In each cohort the first subject enrolled will complete dosing of study medication, and if no significant AEs are observed then the remaining cohort subjects	The subject will be admitted to the study site during the entire dosing period. The schedule of events for this portion of the study is presented in the Time and Events Table. In each cohort, the first subject enrolled will complete the 15-day dosing period and undergo	Clarification of dosing stratification

		may begin dosing one week later. Subjects will have vital sign monitoring during and for 24 hours following each dose of study drug. The Medical Monitor and study PI will be responsible for evaluation of all AE and safety laboratory results.	monitoring for an additional week at the study site. The site and Sponsor Medical Monitors will then review all AE and safety laboratory data. In the absence of any clinically significant AE's the remaining cohort subjects may begin dosing. It is anticipated that the timeframe from last dose of the first cohort subject through AE review will be approximately 2 weeks.	
3 12JUN2013	3.3.4, 3.3.6, 3.3.7	FDA	National Competent Authorities	Term FDA replaced with National Competent Authorities
3 12JUN2013	3.3.8	EDI200 will be thawed to room temperature on the day of dose administration, pooled in syringe(s) and infused via a syringe pump infusion system. The study drug shall be infused routinely over a period of 2 hours, but not to exceed 5 ml/kg/hr or 500 mg EDI200/hr.	EDI200 will be thawed to room temperature on the day of dosing, pooled in syringe(s) and administered via a syringe pump infusion system. The study drug shall be administered by slow IV infusion over at least 30 min, not to exceed 5 ml/kg/hour or 8.5 mg/min EDI200, in order to minimize the risk of infusion-related AE (refer to Investigational Brochure, Section 6.2). For more information on the preparation of EDI200 see the Pharmacy/Investigator Manual.	Clarification of infusion procedure
3 12JUN2013	3.3.8	New text added	During study drug administration and for 24 hrs following infusion the subject will have continuous heart rate and respiratory rate monitoring. A full set of vital signs including temperature, blood pressure, heart rate and respiratory rate will be documented on the following schedule: • Pre dosing - a single set of vital signs within 1 hour of initiating dose infusion	Clarification of continuous monitoring (similar minor changes made throughout protocol)

			• Post dosing: o 15 min after end of infusion, o 1 hr and 4 hrs after end of infusion, o then q4 hrs up to 24 hrs after end of infusion If the unit in which the subject is receiving study drug requires additional monitoring, then that data will be added to the subject's record.	
3 12JUN2013	3.3.8	New text added	The intravenous site will be assessed for patency and signs of local irritation prior to the start of the infusion, every 30 minutes during infusion, and at the end of study drug infusion.	Clarification of infusion site monitoring
3 12JUN2013	4.2.1	The initial physical examination will include assessment of standard developmental milestones, and will be augmented at Months 2, 4 and 6 by the Bayley Scales of Infant Development II (BSID-II), a well-validated assessment tool for use at 1-42 months of age (Black and Matula, 2000).	The initial physical examination will include assessment of standard developmental milestones, and will be augmented at Months 2, 4 and 6 by a validated, standard of care infant assessment tool. Examples of such tools include but are not limited to the Bayley Scales of Infant Development II (BSID-II) and III (BSDI-III) and the Denver Development Screening Test II (DDST II) (Black and Matula, 2000). Whichever tool is selected should be designed for ages down to 2 months of life and should be used for all follow-up visits.	Provision for the use of other tools of development assessment
3 12JUN2013	4.3	To meet inclusion criteria for study drug administration, families of potential study subjects will be asked if their male newborn has been tested for EDA mutations that confirm the XLHED diagnosis, either prenatally or postnatally. If genetic	To meet inclusion criteria for EDI200 administration, potential study subjects are required to have their XLHED diagnosis confirmed by genetic testing of the EDA gene and these test results relayed to the study site. EDA genetic testing itself is outside of the scope of this	Clarification of genetic testing done during screening

		testing has been done, verbal consent from the family will be obtained to provide documentation of test results to the study site via a secure and confidential method including an option for electronic transmission. If not, the study site will provide a genotyping kit with an informed consent form directly to the family (no provision for fetal or amniotic fluid testing as part of this protocol). All genotyping costs will be covered by the study. It will be the responsibility of the family to have cord blood or a neonatal blood sample drawn and sent to the recommended genotyping laboratory.	protocol. If requested, the families of prospective subjects in need of EDA genotyping will be referred to resources available to facilitate this testing. Consent from the family (written or verbal) will be obtained as part of the screening process to provide the study site with documentation of genetic testing results via a secure and confidential method including an option for electronic transmission.	
3 12JUN2013	4.5.1	New text added	It will be the Principal Investigator's responsibility to assess laboratory parameters against local reference ranges and to assess the clinical significance of any out of range values.	Clarification on assessment of lab values using both CTCAE criteria and local reference ranges
3 12JUN2013	4.6.2	The PI will report all SAEs to the Sponsor in a timely fashion, <u>usually</u> within 24 hours of awareness, by completing and faxing the SAE Report Form to CTI Safety as per directions described in the Study Reference Manual.	The PI will report all SAEs to the Sponsor in a timely fashion, within 24 hours of awareness, by completing and faxing the SAE Report Form to CTI Safety as per directions described in the Study Reference Manual.	Word "usually" deleted as reporting requirements are within 24 hours
3 12JUN2013	4.8	Unscheduled DSMB reviews will take place as outlined in Section 3.3.4-3.3.7 for single or accumulated adverse events.	Unscheduled DSMB reviews will take place as outlined in Section 3.3.4-3.3.7 for single or accumulated adverse events. Additional safety-related evaluations of one or more subjects may be requested by the DSMB based on findings through the 6 month, end-of-study visit.	Provision to allow for additional DSMB-requested procedures or visits

3 12JUN2013	5.5	New text added	The Sponsor or DSMB may request unscheduled visits either during the subject's participation in the Study or after his completion. The unscheduled visits may include additional safety-related evaluations (including blood sampling) based on findings through the 6-month, end-of-study visit.	Provision to allow for unscheduled visits
3.1 28OCT2013	3.1.4	Third, they will document pre-treatment ectoderm status related to EDA-A1 deficiency, including sweat duct number, induced sweat volume, presence/absence of dentition on lateral jaw radiograph, dry eyes, digital 2D facial photograph for XLHED facial appearance, thermoregulation imbalance and skin biopsy for expression profile.	Third, they will document pre-treatment ectoderm status related to EDA-A1 deficiency, including sweat duct number, induced sweat volume, presence/absence of dentition on lateral jaw radiograph (supplemented by ultrasound, at the discretion of the PI), dry eyes, digital 2D facial photograph for XLHED facial appearance, thermoregulation imbalance and skin biopsy for expression profile.	Provision for an optional dental ultrasound
3.1 28OCT2013	4.2.7	New text added	At the discretion of the PI the procedure can be supplemented by an ultrasound.	Provision for an optional dental ultrasound

EXECUTIVE SUMMARY

X-linked hypohidrotic ectodermal dysplasia (XLHED) is a disorder of ectoderm development in which sweat and secretory gland hypoplasia predisposes affected infants to serious and potentially life-threatening hyperthermia and pneumonia (Clarke et al., 1987). Those XLHED patients who survive infancy face a host of ectoderm-related clinical conditions including failure to thrive, oligodontia and misshapen teeth, mid-face hypoplasia, eczema, chronic dry eyes, asthma, respiratory infections, sinusitis and chronic nosebleeds. XLHED is caused by inherited defects in the ectodysplasin gene (EDA, www.ncbi.nlm.nih.gov/omim) resulting in a deficiency of the ectoderm signaling protein EDA-A1. As is the general case with X-linked disorders, hemizygous XLHED males are more consistently and severely affected, while heterozygous XLHED females have a more variable phenotype.

In normal development, EDA-A1 acts as an ectoderm signaling molecule that binds specifically to the EDA-A1 receptor (EDAR) triggering initiation and maturation of ectoderm appendages into sweat and secretory glands, tooth buds and hair follicles. In the case of XLHED, EDA-A1 deficiency results in the absence or functional hypoplasia of the ectoderm appendages. There are no therapies currently available for XLHED that prevent or correct the underlying ectodermal abnormalities.

EDI200 is a fully humanized EDA-A1 replacement molecule under development as a novel therapeutic for XLHED. EDI200 comprises the human IgG1 Fc domain linked to the human EDA-A1 receptor-binding domain. In the course of normal ectodermal signaling, EDA-A1 monomers associate as trimers and higher order multimers that are required for activation of the EDA-A1 receptor (EDAR). The N-terminal Fc receptor portion of the EDI200 molecule serves to stabilize the intermolecular EDA-A1 associations required for EDAR binding, and to provide a potential mechanism for transplacental delivery (Miller, 2003).

On-target EDI200 activation of the EDA-A1/EDAR signaling pathway *in vivo* is evidenced by the remarkable phenotypic response in preclinical models. In XLHED-affected animals, EDI200 correction of EDA-A1 deficiency prenatally (mice) or postnatally (newborn mice and dogs) resulted in a significant and sustained improvement in the health of the treated animals (Gaide and Schneider, 2003; Casal et al., 2007; Mauldin et al., 2009). Postnatal studies in both mice and dogs demonstrated a consistent and restricted window of efficacy (Gaide and Schneider, 2003; Edimer Study NCD-11-200-005). These results support the clinical development of EDI200 as a therapeutic to be administered to XLHED-affected patients in the neonatal period or earlier.

This Phase 2 first-in-neonate study will enroll treatment-naïve, XLHED-affected male newborns for EDI200 administration initiated within the first two weeks of life. All subjects will meet entry criteria including documentation of an EDA mutation associated

with XLHED. Following Baseline evaluations, EDI200 dosing will be initiated between day-of-life (DOL) 2 and 14, with each study subject receiving 2 doses/week for a total of 5 doses. This dosing regimen mirrors that used to enhance efficacy in the dog XLHED model, considered to be most relevant to the clinical study design. Comprehensive safety, pharmacokinetic (PK), immunogenicity and pharmacodynamic (PD)/efficacy evaluations of all neonate study subjects will initiate at study enrollment and continue throughout the dosing and follow-up period (to age 6 months).

The study will enroll 6-10 subjects in two cohorts, with a minimum of 3 subjects per cohort. Given the challenge of identifying families where the potential study subject is yet to be born, it is expected that cohort size and time for recruitment will be variable. We anticipate enrolling subjects over a 12-18 month period. Cohort 1 study subjects will each be administered EDI200 IV at 3 mg/kg/dose x 5 doses, equivalent to 0.015 x the neonate no observed adverse effect level (NOAEL) of 200 mg/kg/dose (factor of 1:66) and well below the maximum safe starting dose in initial clinical trials as suggested by FDA guidance. This dose was associated with partial efficacy in the canine XLHED model considered most relevant to the clinical study, and was well tolerated by XLHED adults in the Phase 1 safety study (NCT01564225, www.clinicaltrials.gov)

All safety laboratory studies will be done at the individual study sites and available to the Data Safety Monitoring Board (DSMB) in real time. Following dosing of all subjects in neonate cohort 1, the DSMB will review the cohort 1 safety and PK data. If no new safety issues are identified then cohort 2 subjects will be enrolled and dosed at a ½ log increase to 10 mg/kg/dose IV, equivalent to 0.05 x the neonate NOAEL of 200 mg/kg/dose (factor of 1:20). This dose was associated with enhanced efficacy in the canine XLHED model. Prior to the dosing of XLHED neonates in cohort 2, the DSMB also will have reviewed the safety and PK data from XLHED adult cohort 2 subjects dosed at the same 10 mg/kg/dose and the same 5 dose regimen.

In the core study, primary outcome measures will be safety, PK and immunogenicity. Secondary outcome evaluations of pharmacodynamics (PD)/efficacy will incorporate growth and development parameters, frequency of infections and hospitalizations, facial development as monitored by computerized recognition of XLHED-associated features, and assessments of ectoderm-related physiologic functions using technologies that minimize risk to this population. From 6 months onward (end of data collection in the Phase 2 core study), the EDI200-exposed infants will be enrolled in a long-term extension study with yearly safety and age-appropriate PD/efficacy evaluations.

Male siblings of study subjects, both affected and unaffected, will be offered enrollment in an accompanying natural history sub-study including a medical history questionnaire and a one-time, non-invasive evaluation of current clinical condition (without study drug administration, X-rays or blood draws). The results from these genetically related,

untreated siblings will provide comparative data for interpreting the clinical outcomes in treated study subjects.

SYNOPSIS

Title of Study	A Phase 2 open-label, dose-escalation study to evaluate the safety, pharmacokinetics, immunogenicity and pharmacodynamics/efficacy of EDI200, an EDA-A1 replacement protein, administered to male infants with X-Linked Hypohidrotic Ectodermal Dysplasia (XLHED)
Name of Company	Edimer Pharmaceuticals, Inc.
Name of Finished Product	EDI200
Name of Active Ingredient	EDI200
Protocol Number	ECP-002
IND Number	109262
EudraCT Number	2012-003561-17
Objectives	Primary Objectives • To assess the safety, pharmacokinetics and immunogenicity of EDI200 administered to XLHED-affected neonates Secondary Pharmacodynamic/Efficacy Objectives • To assess EDI200 pharmacodynamics/ efficacy in the treatment of XLHED-affected neonates • To compare clinical and medical history data obtained from untreated male siblings to that of the XLHED-affected neonate receiving study drug
Methodology	Phase 2 open-label, two cohort, dose-escalation study
Number of Subjects	• 6-10 XLHED-affected male neonates for study drug administration • Male siblings (XLHED-affected and unaffected) as historical controls
Diagnosis and Main Criteria for Inclusion	Male neonates documented by genetic diagnosis to carry an EDA mutation associated with XLHED, and their male siblings
Test Product Dose, Route of Administration	3 or 10 mg/kg/dose (IV)
Duration of Treatment	5 doses over 15 days

Pharmacodynamic/Efficacy Evaluations	• Growth and development • Infections and hospitalizations • Dentition • Facial development • Sweat gland number and function • Dry eye assessment • Thermoregulation • Skin biopsy for expression profile
Safety Evaluations	Safety laboratory blood tests, Vital Signs, Adverse Events
Pharmacokinetics Evaluations	Serial blood draws
Statistical Methods	The safety population will consist of all subjects who receive at least one dose of study medication. The PK population will consist of all subjects who receive at least one dose of study medication and have sufficient data points to obtain a plasma concentration by time profile. The PD/efficacy population will consist of all subjects who receive at least one dose of study medication and complete the follow-up assessments through at least month 2.

TIME AND EVENTS SCHEDULE – MULTI-DOSE EDI200 ADMINISTRATION

	Screening		Baseline	Treatment Phase									Follow-up Visits	Study Completion
	Prenatal[1] (Optional)	Postnatal[2] DOL 2 to DOL 12	DOL 2 to DOL 14[3]	TD 0	TD 1	TD 2	TD 4	TD 7	TD 11	TD 14	TD 15	TD 16	TD 21	Mon 2 & 4 of Life[4] (± 1 wk)	Mon 6 of Life[4] (± 2 wks)
Informed Consent	X	X	X												
Inclusion/Exclusion	X	X	X												
Genetic testing			X[5]												
Medical History	X	X[6]	X												
Safety Evaluations															
Physical Examination[7]			X	X	X		X	X	X	X	X		X	X	X
Safety Laboratory			X		X							X	X	X[8]	X
Immunogenicity			X									X		X[8]	X
Pharmacokinetic[9]			X	X	X	X				X		X	X	X[8]	X
PD/Efficacy															
Growth/Development			X											X	X
Dentition[10]			X												
Facial Development[11]			X												X
Sweat Assessments			X											X[8]	X
Dry eye Assessment			X											X[8]	X
Thermoregulation[12]			X										X		
Skin biopsy sample			X		X						X				
Study Drug				X			X	X	X	X					
Adverse Events/Con Meds[13]	X														

TIME AND EVENTS SCHEDULE – MALE SIBLINGS OF STUDY SUBJECTS

	Study Enrollment	Evaluation
	From date of 1st dose study drug administered to affected sibling	Prior to Study Completion for affected sibling
Informed Consent	X	
Inclusion/Exclusion Criteria	X	
Medical History	X	
Safety Evaluations		
Physical Examination		X
Weight, Height, Vital Signs		X
XLHED-associated Outcomes		
Growth/Development		X
Infections/Hospitalizations		X
Dentition		X[14]
Facial Development		X[15]
Sweat Assessments		X
Pulmonary function[16]		X
eNO level[17]		X
Dry eye Assessment[18]		X
Adverse Events & Con Meds	X	

1. Optional prenatal screening enrollment is from end of first trimester through delivery date
2. Newborn's screening window for study inclusion is through DOL #12
3. Baseline evaluations must be completed by DOL #14
4. Follow-up visits at 2, 4 and 6 months of chronologic age
5. In the Screening process, confirmation of subject EDA genotype is required from the family. Under Baseline Events, EDAR genotyping for the phenotype-modifying polymorphism EDAR V370A will be a standard assessment (Cluzeau et al., 2012) but is not required prior to study drug administration
6. Medical history encompasses antenatal and perinatal findings including antenatal ultrasound imaging of tooth buds if performed (Ulm et al., 1998)
7. A full physical examination will be conducted at baseline, day 21, months 2, 4, and 6. With the full physical examination will be the following quantitative assessments: weight, height, head circumference and vital signs (temperature, blood pressure, heart rate and respiratory rate). A brief physical examination will be conducted at treatment days 0, 1, 4, 7, 11, 14 and 15. The brief physical examination will include overall appearance (normal or abnormal and if abnormal why), skin appearance, cardiovascular, pulmonary and abdominal evaluation. With the brief physical examination will be weight and a set of vital signs (temperature, blood pressure, heart rate and respiratory rate). On dosing days vital signs will also be collected pre- and post dosing as described in section 3.3.8.
8. Studies to be performed at 2 months but not at the 4-month visit.
9. PK samples drawn pre-EDI200 dosing and post-end of infusion at approximately the following time points:

	Pre-Dose	Post-Dose							
		15 (±5) min	3 (±.5) hrs	8 (±1) hrs	18 (±2) hrs	24(±2) hrs	48 (±4) hrs	168(±8) hrs	Age 2 months (±1 wk) & 6 months (±2 wks)
D0 (dose 1)	X	X	X	X		X	X		
D14 (dose 5)	X	X	X		X		X	X	X

10. Baseline lateral jaw film only. Dental evaluation to be performed in the long-term extension study will minimize the use of dental radiographs, and allow for substitution of dental imaging obtained as part of the routine care of XLHED patients.

11. Digital analysis of non-invasive 2D facial photographs is a technology under development jointly by the Sponsor and a private company and is being explored as a tool for monitoring change in craniofacial appearance. The algorithm assesses the subject's facial structures in the neonatal period and continues through photographs taken in the extension study.
12. Thermoregulation assessment in the neonatal period is a well-documented procedure monitoring short-term temperature and vital sign response in a closed system (incubator). At an older age in the extension study, exercise-related thermoregulation will be assessed.
13. Infections/hospitalizations as PD/efficacy endpoint will be captured through adverse events
14. No dental radiographs will be taken as part of this sibling sub-study. Subjects will be asked to provide copies of recent dental X-rays from an outside source.
15. Frontal and lateral facial photographs to be taken and baby picture (age up to 1 month) to be collected if available
16. Minimum age 5 years for pulmonary testing
17. Minimum age 4 years for eNO assessment
18. A more comprehensive dry eye assessment will be performed in children as opposed to the neonates

LIST OF ABBREVIATIONS

Abbreviation	Definition
2D	Two Dimensional
ADL	Activities of Daily Living
AE	Adverse Event
AUC	Area Under the Curve
BSID	Bayley Scales of Infant Development
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTGF	Connective Tissue Growth Factor
DDST	Denver Development Screening Test
DOL	Day of Life
DSMB	Data Safety Monitoring Board
EDA	Ectodysplasin A
EDA-A1	Ectodysplasin protein A1
EDAR	Ectodysplasin-A1 Receptor
EDC	Electronic Data Capture
eCRF	Electronic Case Report Forms
eNO	Exhaled Nitric Oxide
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
Lgr5	Leucine-Rich G-Protein Coupled Receptor
MedDRA	Medical Dictionary for Regulatory Activities
NCD	Nonclinical Document
NCI	National Cancer Institute
NOAEL	No Adverse Effect Level
OSDI	Ocular Surface Disease Index
PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetic
RNA	Ribonucleic Acid
SAE	Serious adverse event
Shh	Sonic Hedgehog

SUSAR	Suspected Unexpected Adverse Reaction
TD	Treatment Day
XLHED	X-Linked Hypohidrotic Ectodermal Dysplasia

PI AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the conduct of the study.

_____

PI's Signature* Date

_____

Name of PI (Typed or Printed)

_____

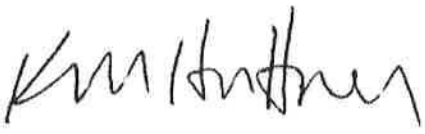
_____

_____

Institution Address*

_____

Phone Number*



28OCT2013

Sponsor's Medical Monitor Signature Date

Kenneth Huttner, MD, PhD

Name of Medical Monitor (Typed or Printed)

* If the address or phone number of the PI changes during the course of the study, written notification will be provided by the PI to the Sponsor and will not require protocol amendment(s).

1 BACKGROUND

XLHED, the most common of the ectodermal dysplasias, is caused by inherited defects in the ectodysplasin (EDA) gene that disrupt synthesis and/or function of the primary translational product EDA-A1 (www.ncbi.nlm.nih.gov/omim). In normal development, EDA-A1 acts as an ectoderm signaling molecule that binds specifically to the EDA-A1 receptor (EDAR) triggering initiation and maturation of ectoderm appendages into sweat and secretory glands, tooth buds and hair follicles. The absence of normal EDA-A1 expression results in sweat and secretory gland hypoplasia predisposing XLHED-affected infants to serious and potentially life-threatening hyperthermia and pneumonia (Clarke et al., 1987). XLHED-affected children surviving infancy face a host of life-long ectoderm-related clinical conditions including failure to thrive, oligodontia and misshapen teeth, mid-face hypoplasia, eczema, chronic dry eyes, asthma, respiratory infections, sinusitis and chronic nosebleeds. As is the general case with X-linked disorders, XLHED-affected males are more consistently and severely affected, while XLHED-affected females have a more variable phenotype.

There are no therapies currently available for XLHED that prevent or correct the underlying abnormalities of ectoderm-derived structures. In two genetically confirmed animal models of XLHED, systemic administration of recombinant EDA-A1 (EDI200) in the prenatal (mice) or postnatal (newborn mice and dogs) settings corrected many of the defects in ectoderm development resulting in a significant and sustained improvement in the health of the treated animals (Gaide and Schneider, 2003; Casal et al., 2007). To date, data in both species has demonstrated a restricted efficacy window that closes after the first several weeks of postnatal life (Gaide and Schneider, 2003; Edimer Study NCD-200-11-005). This is consistent with the well-studied timeframe for ectoderm appendage development, and supports the clinical development of EDI200 as a therapeutic to be administered to XLHED-affected patients in the newborn period or earlier.

1.1 Rationale for Study

Study Drug - EDI200 is a fully humanized EDA-A1 replacement molecule designed for parenteral administration, comprising the human IgG1 Fc sequence linked to the human EDA-A1 receptor-binding domain. The N-terminal Fc receptor portion of the EDI200 molecule serves to facilitate and stabilize the intermolecular associations required for EDAR binding, as well as providing a potential mechanism for fetal delivery (Miller, 2003). Through its unique design, EDI200 retains the EDA-A1 receptor specificity as evidenced by the targeted phenotype response in preclinical XLHED models (Gaide and Schneider, 2003; Casal et al., 2007; Mauldin et al., 2009).

Safety and PK data in Adults - Following discussions with the FDA regarding the clinical development plan for EDI200 in a pediatric indication; a Phase 1 study in XLHED-affected adults was initiated (NCT01564225, www.clinicaltrials.gov) to develop human safety and PK data in anticipation of dosing XLHED-affected neonates. Selecting XLHED-affected adults for

the Phase 1 study provided a genetic and biologic relevance to XLHED-affected neonates. Enrolling adult XLHED-affected males and females: (1) supported dosing of male XLHED neonates in the current trial; (2) provided data for the possibility of dosing XLHED-affected female neonates; and (3) initiated the collection of data necessary to support a future trial of maternal EDI200 administration. Identical dosage (mg/kg) and dosing regimens are planned for the adult and neonate XLHED studies.

Neonate Dosing Strategy: Age at Dosing Initiation; Dosing Regimen; Starting Dose

Age at Dosing Initiation – In both the mouse and dog XLHED models; early postnatal administration was associated with correction of clinically relevant abnormalities. Based primarily on the multi-dose dog data, study drug administration in this protocol is targeted to begin between day-of-life (DOL) #2 and DOL #14 (Edimer Study NCD-200-11-005).

Dose Regimen - The EDI200 dosing regimen proposed for the Phase 2 XLHED neonate study is a single course consisting of 5 doses administered at 2 doses/week. This regimen is based on results from the dog XLHED model which is most comparable to the human condition in developmental maturity at birth and in health-related endpoints (Casal et al., 2007; Edimer Study NCD-200-11-004). The 2-dose/week-regimen was incorporated into the GLP toxicology studies as well (Edimer Studies 1800-009 and 1800-010).

Starting Dose – No study-drug related adverse effects were observed at the highest EDI200 dose tested in both mouse and dog neonatal GLP toxicology studies, confirming a NOAEL of ≥200 mg/kg/dose (1800-009; 1800-010). Consistent with FDA guidelines for Maximum Starting Dose in Initial Clinical Trials, and incorporating a conservative approach to dosing in this vulnerable population, the first cohort of XLHED neonates will receive EDI200 at 3 mg/kg/dose IV, 0.015 x neonatal NOAEL (factor of 1/66). In the dog XLHED efficacy studies, dosing at 3 mg/kg/dose was associated with partial efficacy, which was enhanced significantly in animals receiving 10 mg/kg/dose (Edimer Study NCD-200-11-004). Safety and PK data from the Phase 1 adult study cohort treated with EDI200 at 3 mg/kg/dose x 5 doses over 15 days was reviewed by the DSMB with no reported study drug-related adverse events.

In the Phase 2 neonate study, the DSMB will review safety and PK data from neonate cohort 1, and in the absence of safety concerns, neonates will then be enrolled in cohort 2 and dosed at a pharmacologic half-log increase to EDI200 10 mg/kg/dose IV, equivalent to 0.05 x the neonatal NOAEL (factor of 1/20). Safety and PK data from the Phase 1 adult cohort 2, having received EDI200 at the same dose and the same dosing regimen, also will be reviewed by the DSMB prior to initiating dosing in neonate cohort 2. The dose for XLHED neonate cohort 2 is anticipated to maximize postnatal EDI200 efficacy based on the dog XLHED results (Edimer Study NCD-200-11-004).

Cohort enrollment - The Phase 2 neonate XLHED study is designed to enroll two cohorts of at least 3 subjects each (cohort size determined by rate of enrollment and sponsor discretion),

consistent with the practical aspects of study enrollment in ultra-rare orphan disorders and the unique challenge of enrolling newborns. Enrollment and dosing of all subjects in neonate cohort 1 (3 mg/kg/dose) will be completed and reviewed prior to initiating dosing of subjects in neonate cohort 2 (10 mg/kg/dose).

Primary objectives - Safety labs, physical examination, vital signs, adverse events and concomitant medications, immunogenicity, and PK will be documented as outlined in the Time and Events schedule. The schedule for PK sampling, based on the preclinical and Phase 1 adult XLHED dosing results, incorporates a sparse sampling approach to limit the frequency and volumes of neonatal blood draws. The proposed PK sampling maximizes data collection for determining both the AUC and Cmax.

Pharmacodynamic/efficacy objectives - PD/efficacy endpoint assessments relevant to the biology and pathophysiology of XLHED are incorporated into the study design as outlined in the Time and Events:

- *Clinical endpoints* - growth and development (including feeding history), infections and hospitalizations (captured under adverse events).
- *Imaging assessments* - diagnostic dental radiographs (the post-treatment dental X-rays will be incorporated into the long-term extension study and hence are not described further in this protocol), antenatal ultrasound results for tooth bud development (if available as part of Obstetric care, documented in the Medical History), pre- and post-treatment facial photographs to assess changes in craniofacial features associated with XLHED and its correction.
- *Clinical biomarkers* - sweat duct number and induced sweat volume, thermoregulation and dry eye evaluation.
- *Molecular biomarkers* - skin biopsy for expression profile.

All affected and unaffected male siblings of study subjects will be offered enrollment in a natural history sub-study evaluating the medical history and clinical condition of genetically related, untreated comparators for the study subjects.

Study Duration - Total study duration for each subject receiving study drug will be approximately 6 months, including a treatment and safety/efficacy monitoring period. A long-term extension study for all subjects receiving study drug will continue safety and PD/efficacy evaluations. Study duration for male siblings in the sibling sub study will be 1-2 days.

2 OBJECTIVES

2.1 Primary Objectives

To assess the safety, pharmacokinetics and immunogenicity of EDI200 administered to XLHED-affected neonates

2.2 Pharmacodynamic/Efficacy Objectives

- To assess the pharmacodynamics/efficacy of EDI200 administered to XLHED-affected neonates
- To compare clinical data and medical history obtained from untreated male siblings to that of the XLHED-affected neonates receiving study drug

3 STUDY DESIGN

3.1 Multi-Dose EDI200 Administration

3.1.1 *Brief Description and Rationale for Study Design*

X-linked hypohidrotic ectodermal dysplasia (XLHED) is a disorder of ectoderm development associated with EDA gene mutations that lead to a deficiency of the ectoderm signaling protein EDA-A1. EDI200 is a fully humanized EDA-A1 replacement molecule under development as a novel therapeutic for XLHED. In two XLHED animal models, a single course of perinatal EDI200 administration resulted in a substantial correction of abnormalities in ectoderm development and a significant improvement in the health of the treated animals (Gaide and Schneider, 2003; Casal et al., 2007). These preclinical findings support the clinical development of EDI200 as a therapeutic to be administered to XLHED-affected patients in the neonatal period or earlier.

The open-label Phase 2 study of EDI200 administered to XLHED-affected neonates will enroll 6-10 subjects in two sequential cohorts. Each study subject will have documentation of an EDA gene mutation. Cohorts will be enrolled sequentially, i.e. the first subjects will all be enrolled in cohort 1, and only after cohort 1 safety evaluation by the DSMB will subjects be enrolled in cohort 2 for dosing at a higher level. Final cohort size will be determined by subject and site availability, with at least 3 subjects per cohort.

The EDI200 dose for subjects in cohort 1 is 3 mg/kg/dose, consistent with the FDA Guidelines for Maximum Safe Starting Dose in Initial Clinical Trials based on the neonate NOAEL of $\geq$200 mg/kg/dose. This dose is anticipated to be associated with partial efficacy based on the dog XLHED studies. Safety laboratory results will be available to the DSMB in real time, and a formal DSMB safety and PK review will occur following completion of dosing in cohort 1. Additionally, the DSMB will have available to it safety and PK data from all XLHED-affected adult subjects from the Phase 1 adult safety study (NCT01564225, www.clinicaltrials.gov). In the absence of a safety signal or PK concern from DSMB review, XLHED neonates in cohort 2 will be dosed at 10 mg/kg/dose, a half-log pharmacologic increase to a dose anticipated to maximize clinical benefit based on the XLHED dog studies.

Primary outcome measures for all subjects will be safety, PK and immunogenicity. Study duration is 6 months with all subjects rolling over into a long-term extension study providing yearly evaluations. Pharmacodynamic/efficacy objectives in the Phase 2 neonate study will be limited by the timeline for ectodermal development that often exceeds 6 months, e.g. dentition. Therefore, several of these endpoints will be incorporated into the extension study protocol. There will be assessment of the following: (1) endpoints relevant to the common clinical findings in XLHED using age-appropriate technologies, e.g. growth and development, infections and hospitalizations, sweat duct counts and stimulated sweat production, pre-treatment dentition, and thermoregulation; (2) change from baseline in craniofacial structures

using a non-invasive facial recognition software program based on subject digital facial photographs (Appendix 1); and (3) change in molecular expression profile using skin biopsy samples obtained pre- and post-study drug exposure.

3.1.2 *Starting and Target Dose/Dosing Regimen*

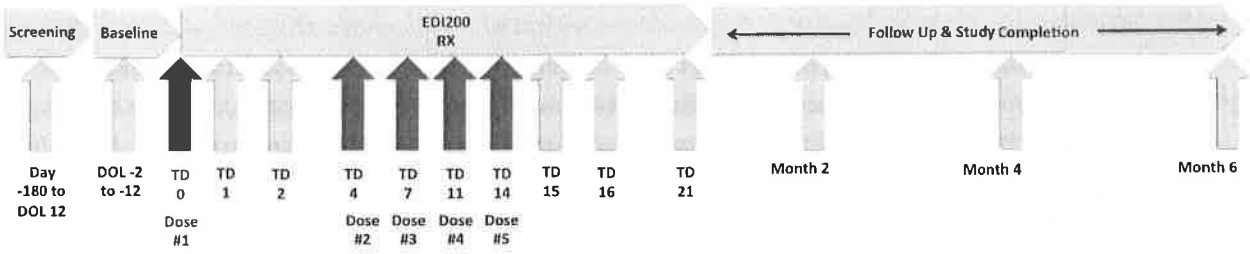
The proposed starting dose is consistent with the FDA Guidelines for Maximum Safe Starting Dose in Initial Clinical Trials, based on the neonate GLP toxicology studies in two species that demonstrated a NOAEL of ≥200 mg/kg (MPI Study 1800-009 and 1800-010). Cohort 1 subjects will be dosed with EDI200 at 3 mg/kg/dose IV, 0.015 x neonate NOAEL (factor of 1/66). The proposed dosing regimen of 2 doses/week x 5 doses, beginning within the first 2 weeks of life, is supported by the dosing regimen in the GLP toxicology studies. This dose and dosing regimen is in the range of anticipated partial efficacy in the dog XLHED model, considered the most relevant species for endpoint assessment.

Prior to enrolling subjects in neonate cohort 1, the DSMB reviewed safety and PK data from cohort 1 in the Phase 1 XLHED study (NCT01564225) where adult XLHED subjects were administered EDI200 at the same dose (3 mg/kg/dose) and dosing regimen (5 doses total at 2 doses/week). No study drug-related adverse events were reported. In neonate cohort 1, the first subject enrolled will complete dosing followed by a ~2-week safety review. If no safety concerns are observed, the remaining cohort 1 subjects will begin dosing. Dosing for individual subjects will be on a mg/kg basis.

Once all subjects in neonate cohort 1 have received their IV dosing, the DSMB will review safety and PK data. In the absence of safety concerns following DSMB review of cohort 1 data, neonates in cohort 2 will be dosed at a pharmacologic half-log increase to 10 mg/kg/dose, 0.05 x neonate NOAEL (factor of 1/20), following the same 5-dose regimen (see figure below). The dose and dosing regimen for neonate cohort 2 is in the range anticipated to maximize postnatal efficacy based on results from the dog XLHED model. Dosing of subjects in cohort 2 is sequential as described in cohort 1. Subject enrollment and cohort initiation will be according to the following schedule:

The study will be conducted in age-appropriate clinical facilities by medical staff with appropriate levels of training and expertise and an understanding of the investigational medicinal product, its target and mechanism of action. There will be immediate access to facilities for the treatment of medical emergencies including an Intensive Care Unit.

The study timeline and visit dates for each subject are as follows:



3.1.3 *Screening*

A family with a male fetus/newborn with a clinical suspicion of XLHED may inquire to receive study information by phone, email or directly at a study site (also available on www.clinicaltrials.gov). If the family then wishes to be considered for study participation, they have the following options:

1. Prenatal Screening Enrollment (optional): the family of a male fetus at risk for XLHED may provide Informed Consent (ICF1) for data collection to begin in order to evaluate eligibility for newborn EDI200 treatment (see Sections 3.3.1 and 3.3.2). Entering the screening process early will allow for discussion and planning to minimize the potential family disruption that is likely to accompany early postnatal transfer to the study site if the subject is to be enrolled in the treatment protocol. The language of ICF1 will state clearly that once all Inclusion/Exclusion (I/E) criteria are met, an additional Informed Consent (ICF2), obtained postnatally, will be required in order to enroll the XLHED-affected neonate into the treatment portion of the study. The enrollment window for treatment encompasses the period from DOL #2 through DOL #12 (allowing a minimum of two days for transfer to the study site and baseline assessments prior to DOL #14, the last day study drug dosing can be initiated).

2. Postnatal Screening Enrollment: in the absence of Prenatal Screening Enrollment, the family of a male newborn at risk for XLHED may provide Informed Consent (ICF1) for data collection to begin in order to evaluate eligibility for the newborn EDI200 treatment (see Sections 3.3.1 and 3.3.2). The language of ICF1 will state clearly that once all Inclusion/Exclusion (I/E) criteria are met, an additional Informed Consent (ICF2) will be required in order to enroll the XLHED-affected neonate into the treatment portion of the study. The enrollment window for treatment encompasses the period from DOL #2 through DOL #12 (allowing a minimum of two days for transfer to the study site and baseline assessments prior to DOL #14, the last day study drug dosing can be initiated).

A key inclusion criterion for the treatment protocol is verification of the XLHED diagnosis through EDA mutation testing. As part of the screening process, genetic testing results may be provided by the family to the study site via a secure and confidential method including the option for electronic transmission. If genotyping confirmation is not available at the time of

Screening Informed Consent, the families of prospective subjects will be referred to resources available to facilitate rapid genotype testing at an accredited laboratory.

Families may be considering delivery at a clinical study site to facilitate treatment of their XLHED-affected son as soon as possible after birth. Any such decision is outside of this protocol and would be a private matter between the family, their health care providers, their insurance company, and the delivery service at the study site. Delivery at the study site would not commit the family to have their newborn participate in the treatment protocol, nor would it commit the PI and study site to enroll the XLHED-affected male neonate unless and until he met all the required I/E criteria and a treatment Informed Consent (ICF2) was signed by both parents (if reasonably available).

If the XLHED-affected neonate meeting inclusion/exclusion criteria is not born at the study site, the study team will assist in and cover all reasonable expenses associated with his transfer to the site. If medical transport is required, this will occur under specific Informed Consent (ICF-T) requiring signatures of both parents (if reasonably available). The window for transfer to the study site must allow for the neonate to complete Baseline evaluations in a timely manner prior to DOL #14.

3.1.4 *Baseline*

Baseline evaluation will begin with confirmation of treatment inclusion/exclusion criteria and documentation of relevant family, pregnancy and neonatal medical history. Baseline assessments of the XLHED-affected male infant as described below are to be completed prior to first dose study drug. To date, there is little data published describing evaluation techniques for XLHED patient in the newborn period. The Sponsor has experience with using the novel, minimally invasive technologies that are incorporated into this study protocol (www.edimerpharma.com/Publications and News/Publications and Abstracts)

In this Phase 2 protocol, baseline assessments of the neonate study subjects will serve three purposes. First, they will verify the general health of the XLHED-affected infant including documentation of developmental status and full physical examination. Second, blood samples will be collected for pre-treatment safety laboratory values, documentation of the absence of EDI200 and anti-EDI200 antibodies, and genotyping of the EDAR V370A polymorphism that has the potential to modify the XLHED-phenotype. Third, they will document pre-treatment ectoderm status related to EDA-A1 deficiency, including sweat duct number, induced sweat volume, presence/absence of dentition on lateral jaw radiograph (supplemented by ultrasound, at the discretion of the PI), dry eyes, digital 2D facial photograph for XLHED facial appearance, thermoregulation imbalance and skin biopsy for expression profile.

3.1.5 *Treatment Period*

The subject will be admitted to the study site during the entire dosing period. The schedule of events for this portion of the study is presented in the Time and Events Table. In each cohort, the first subject enrolled will complete the 15-day dosing period and undergo monitoring for an additional week at the study site. The site and Sponsor Medical Monitors will then review all AE and safety laboratory data. In the absence of any clinically significant AE's the remaining cohort subjects may begin dosing. It is anticipated that the timeframe from last dose of the first cohort subject through AE review will be approximately 2 weeks.

Each subject will be administered 5 doses of EDI200, administered IV on Treatment Days (TD) 0, 4, 7, 11 and 14, with vital sign monitoring during and for 24 hours following each dose of study drug. The Treatment Day for doses two through five may be ± 1 day, but doses must be at least 48 hours apart. Subjects in cohort 1 will be dosed at 3 mg/kg/dose calculated on Baseline weight.

On TD 0, subjects will have the following evaluations performed prior to dosing: brief physical exam, AE and concomitant medication assessment. Subjects will be administered dose 1 of study drug with vital sign monitoring during and for 24 hrs post-dose. Full details of the vital sign monitoring plan are described in Section 3.3.8. Sparse PK sampling time points post-dosing are described in Section 4.5.2.

On TD 1, subjects will have the following evaluations performed: brief physical exam, AE and concomitant medication assessment, safety laboratories, PK sampling and skin biopsy for expression profile (both approximately 24-hour post dose 1).

On TD 2, subjects will have the following evaluations performed: AE and concomitant medication assessment and PK sampling (approximately 48-hour post dose 1).

On TD 4, subjects will have the following evaluations performed prior to dosing: brief physical exam, AE and concomitant medication assessment. Subjects will be administered dose 2 of study drug with vital sign monitoring during and for 24 hrs post-dose.

On TD 7, subjects will have the following evaluations performed prior to dosing: brief physical exam and AE and concomitant medication assessment. Subjects will be administered dose 3 of study drug with vital sign monitoring during and for 24 hrs post-dose.

On TD 11, subjects will have the following evaluations performed prior to dosing: brief physical exam and AE and concomitant medication assessment. Subjects will be administered dose 4 of study drug with vital sign monitoring during and for 24 hrs post-dose.

On TD 14, subjects will have the following evaluations performed prior to dosing: brief physical exam and AE and concomitant medication assessment, and PK sampling. Subjects will

be administered dose 5 of study drug with vital sign monitoring during and for 24 hrs post-dose. Sparse PK sampling time points post-dosing are described in Section 4.5.2.

On TD 15, subjects will have the following evaluations performed: brief physical exam, AE and concomitant medication assessment, and a skin biopsy obtained approximately 24 hours after administration of the last dose of study drug.

On TD 16, subjects will have the following evaluations performed: AE and concomitant medication assessment, safety laboratories, immunogenicity sampling, and PK sampling (approximately 48-hour post dose 5).

On TD 21, subjects will have the following evaluations performed: full physical examination, AE and concomitant medication assessment, post-treatment thermoregulation assessment, safety laboratories and PK sampling (approximately 168-hour post dose 5).

The remainder of the study procedures through Month 6 are described in the post-treatment section, Section 3.1.6.

Dose escalation in XLHED neonate cohort 2 will not occur until a review of safety and PK data from XLHED neonate cohort 1 has been completed by the DSMB, approximately three weeks after the last subject is dosed in cohort 1. Assuming no safety or PK concerns following DSMB review, subjects in XLHED neonate cohort 2 will be dosed with EDI200 at 10 mg/kg/dose IV, a pharmacologic half-log increase. As part of the safety-monitoring program, prior to dosing subjects in neonate cohort 2 the DSMB will have reviewed safety and PK data from adult cohort 2 in the Phase 1 adult XLHED study where subjects received EDI200 at the same dose (10 mg/kg/dose) and dosing regimen (5 doses total at 2 doses/week).

3.1.6 *Post-Treatment Follow Up*

The post-treatment visits at Months of Life 2, 4 and 6 are designed to capture safety, immunogenicity and PD/efficacy data at appropriate timepoints following study drug exposure. In addition, PK data will be collected at Months of Life 2 and 6 visits. The post-treatment frequency of visits to the study site represents a balance between the acquisition of informative data and minimizing the travel stresses for the infant subject and his family. These evaluations will not supplant the subject's normal well-child care visits and immunizations by his primary care provider.

At Month 2 of life, subjects will have the following evaluations: full physical exam, AE and concomitant medication assessment, safety laboratories, PK and immunogenicity sampling, and PD/efficacy evaluations including growth and development, induced sweating and sweat duct imaging and dry eye evaluation. Expected stay at the study site location (i.e. within the vicinity of the study site) is 1-2 days.

At Month 4 of life, subjects will have the following evaluations: full physical exam, AE and concomitant medication assessment, and PD/efficacy evaluations including growth and development. Expected stay at the study site location (i.e. within the vicinity of the study site) is 1-2 days.

At Month 6 of life, subjects will have the following evaluations: full physical exam, AE and concomitant medication assessment, safety laboratories, PK and immunogenicity sampling, and PD/efficacy evaluations including growth and development, induced sweating and sweat duct imaging, dry eye assessment and digital facial photographs. Expected stay at the study site location (i.e. within the vicinity of the study site) is 1-2 days.

The conclusion of the core study is defined as the last visit of the last participant.

3.2 XLHED-Affected and Unaffected Male Siblings of Study Subjects

All male siblings (including multiple male siblings of a singe neonate) of enrolled XLHED-affected neonates will be offered the opportunity to participate in a non-invasive evaluation providing historical control data for this open-label study. The technologies involved will be modeled on the core study evaluations, with the exception that no X-rays will be taken; no blood draws and no tissue sampling will be involved. The evaluations will take place at the study site and will include Informed Consent and Assent, if applicable, medical history, physical examination, vital signs including weight and height, digital facial photographs (frontal and lateral), growth and development assessments, induced sweating and sweat duct imaging, pulmonary function testing and eNO levels when age-appropriate (see Time & Events Schedule), dry eye evaluation and dental examination. Siblings will be asked to provide copies of their most recent dental radiographs. Expected stay at the study site location (i.e. within the vicinity of the study site) is 1-2 days.

3.3 Study Subjects

This Phase 2 study will enroll 6-10 XLHED-affected male neonates for study drug administration, and includes the optional enrollment of all male siblings, both affected and unaffected, for non-invasive evaluations.

3.3.1 *Inclusion Criteria*

Subjects for study drug administration must meet all of the following criteria to be enrolled:

1. Male with genetic confirmation of an XLHED diagnosis.
2. Subject must be at least 48 hours age and no older than 14 days.
3. Subject will have reached term (defined as 37 weeks gestation or older) prior to receiving first dose study drug.

4. Written informed consent of both parents (if reasonably available) must be obtained for treatment of their XLHED-affected male infant.
5. Neither mother nor the XLHED-affected male infant known to have received an investigational study drug in the 9 months prior to study subject enrollment in this study.
6. No major medical issues that the PI considers a contraindication to participation.

Male siblings of subjects receiving study drug must meet all of the following criteria to be enrolled in the natural history sub-study (no age limit involved):

1. Provide written informed consent/assent.
2. A full or half-sibling of a study subject where the study subject has received at least one dose of study drug in the Phase 2 XLHED Neonate Study and has not yet completed the study.
3. No major medical issues that the PI considers a contraindication to participation.

3.3.2 *Exclusion Criteria*

Subjects for study drug administration who meet any of the following criteria cannot be enrolled in this study:

1. Medically significant postnatal complications or congenital anomalies outside of those considered associated with the diagnosis of XLHED.

Male siblings of subjects receiving study drug who meet any of the following criteria cannot be enrolled in the natural history sub-study:

1. Known hypersensitivity to pilocarpine or pilocarpine-like muscarinic agonists.
2. Known hypersensitivity to lidocaine or lidocaine-like agents.
3. Presence of pacemaker.
4. Subjects who are not able or are not willing to comply with the procedures of this protocol.
5. Subject has a condition, which in the opinion of the PI would not allow for safe conduct of the study.

3.3.3 *Withdrawal or Removal of Subjects from the Study*

Study subjects/guardians may elect to discontinue study subject participation and withdraw from the study at any time without prejudice. The PI or Sponsor may withdraw a subject from participation in this study for any of the following reasons:

- A protocol violation occurs,
- The subject is not compliant with study procedures,
- A serious or intolerable adverse event occurs,
- The Sponsor or PI terminates the study, or
- The subject/guardian requests to be discontinued from the study.

A discontinuation occurs when an enrolled subject ceases participation in the study prior to completion of the protocol, regardless of the circumstances. The PI will determine the primary reason for discontinuation, and it will be recorded in the case report form and in the subject's research record. A discontinuation must be reported immediately to the Sponsor if it is due to a serious adverse event. The PI will provide or arrange for appropriate follow-up for such subjects (if required), and document the course of the subject's condition. In all cases of subject discontinuation, an attempt should be made to obtain the End-of-Study evaluations at their last study visit.

3.3.4 *Subject, Cohort or Study Suspension/Termination*

The Sponsor and/or the DSMB have the right to close this study at any time for safety or administrative reasons, although this should occur only after consultation between involved parties. The IRB/IEC and all relevant local National Competent Authorities must be informed.

3.3.5 *Subject Stopping Criteria*

- All AE and safety laboratory results will be available to the Medical Monitor, PI and DSMB in real time.
- For any Grade 2 or 3 adverse event (AE) defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v4.0; Appendix 2) that is deemed possibly, probably or definitely related to study drug treatment, individual subject dosing will be held pending review and recommendations of the Medical Monitor.
- If a subject misses a single dose and then is restarted, that dose will not be made up but all subsequent doses will be administered on schedule.
- If a subject misses two consecutive doses then dosing will not be restarted, but all study follow-up visits will occur as originally scheduled.

3.3.6 *Cohort Stopping Criteria*

The study design has only one cohort being dosed with study drug at any given time. Dosing of all subjects within a cohort will be suspended for:

- Two or more individuals develop a Grade 2 or 3 AE in a similar system organ class deemed possibly, probably or definitely related to study drug treatment (CTCAE v4.0), or
- For any Grade 4 adverse event (classified as severe or life-threatening) or a serious adverse event (SAE), regardless of drug-relatedness.

In the case where cohort dosing has been suspended, DSMB review of the AEs with the Medical Monitor, study PI and Sponsor will be required prior to discussing with a subject's family the option of restarting study drug or to enrolling additional subjects in the cohort. Missed doses will not be made up. Any subject missing two consecutive doses will not be restarted on treatment, will not be considered to have completed the dosing regimen, but will have all study follow-up visits as originally scheduled. If the DSMB safety review concludes that cohort dosing may continue, an additional subject may be added to the cohort for each subject that does not complete the dosing regimen.

In the case where a DSMB safety review concludes that a cohort should not continue dosing, no additional doses will be administered to subjects in that cohort, no additional subjects will be enrolled in that cohort, and all follow-up visits for enrolled subjects will occur as originally scheduled. The Sponsor will notify both the relevant National Competent Authorities and the local IRB/IEC of the action taken. The scheduled dose escalation cohorts will be suspended, although a more conservative dose escalation strategy may be considered for a subsequent cohort, requiring DSMB, relevant National Competent Authorities and study site IRB/IEC approval.

3.3.7 *Study Stopping Criteria*

The Sponsor and/or the DSMB have the right to close this study at any time for safety or administrative reasons, with timely notification of the relevant National Competent Authorities.

Permanent halting of dosing in any cohort by the DSMB related to safety concerns will trigger an automatic review of study termination by the DSMB in communication with the Medical Monitor, study PI, and Sponsor. If it is determined that study dosing should be terminated, all follow-up visits will occur as originally scheduled for subjects having received one or more doses of study drug. Study Sponsor assumes responsibility for reporting premature study termination to all regulatory authorities and institutional review boards.

Should the study be closed prematurely, all study materials (except documentation that has to remain stored with the PI) must be returned to the Sponsor. The PI will retain all other documents until notification given by the Sponsor for destruction.

3.3.8 *Treatment*

EDI200 study drug will be provided as a sterile solution for intravenous infusion in 3 ml glass vials, approximately 2.1 ml/vial at a concentration of approximately 5 mg/ml. Vials will be labeled according to local regulations and Sponsor standards. All study drug supplies should be stored frozen at -60 °C to -90 °C.

Dosing of EDI200 will vary by cohort. Study drug administration will be as follows:

Cohort	Number of subjects	Dose	Number of Doses	Study Day of Administration
Cohort 1	3-7	3 mg/kg	5	0, 4, 7, 11, 14
Cohort 2	3-7	10 mg/kg	5	0, 4, 7, 11, 14

The weight used to calculate study drug dose will be the subject's Baseline weight for all doses. If during the treatment period a subject experiences a change in weight of >10% from Baseline, the PI(s) and the Medical Monitor will review the option of adjustments to the subject's dosing.

EDI200 will be **thawed to room temperature** on the day of dosing, pooled in syringe(s) and administered via a syringe pump infusion system. The study drug shall be administered by slow IV infusion over at least 30 min, not to exceed 5 ml/kg/hour or 8.5 mg/min EDI200, in order to minimize the risk of infusion-related AE (refer to Investigational Brochure, Section 6.2). For more information on the preparation of EDI200 see the Pharmacy/Investigator Manual.

Examples are shown in the table below.

Subject Weight	EDI200 Dose (mg/kg)	Total Dose EDI200	EDI200 Conc (mg/ml)	Vol	Vol/kg	Minimum Infusion Time	ml/kg/ hr	EDI200 mg/min
3 kg	3	9 mg	5	1.8 ml	0.6 ml/kg	0.5 hrs	1.2	0.3
3 kg	10	30 mg	5	6 ml	2.0 ml/kg	0.5 hrs	4	1.0
4 kg	3	12 mg	5	2.4 ml	0.6 ml/kg	0.5 hrs	1.2	0.4
4 kg	10	40 mg	5	8 ml	2.0 ml/kg	0.5 hrs	4	1.3
5 kg	3	15 mg	5	3 ml	0.6 ml/kg	0.5 hrs	1.2	0.5
5 kg	10	50 mg	5	10 ml	2.0 ml/kg	0.5 hrs	4	1.7

During study drug administration and for 24 hrs following infusion the subject will have continuous heart rate and respiratory rate monitoring. A full set of vital signs including temperature, blood pressure, heart rate and respiratory rate will be documented on the following schedule:

- Pre dosing - a single set of vital signs within 1 hour of initiating dose infusion
- Post dosing:
  - 15 min after end of infusion,
  - 1 hr and 4 hrs after end of infusion,
  - then q4 hrs up to 24 hrs after end of infusion

If the unit in which the subject is receiving study drug requires additional monitoring, then that data will be added to the subject's record.

The intravenous site will be assessed for patency and signs of local irritation prior to the start of the infusion, every 30 minutes during infusion, and at the end of study drug infusion.

Doses 2-5 are scheduled for study days 4, 7, 11 and 14 respectively in both cohorts. If the subject is unable to be dosed on the specified day, a window of $\pm$24 hours is acceptable. However, there must be a minimum of two days between any two doses. The calendar date and 24-hour clock time of the beginning and end of each infusion will be recorded on the CRF. The dates and timing of PK sampling around dose 5 will be adjusted for any change in dosing schedule.

It is the responsibility of the clinical investigator to ensure that all study drug received at the site will be inventoried and accounted for throughout the study. Study drug must be handled strictly in accordance with the protocol and the container label and will be stored in a limited access area under appropriate environmental conditions. The investigator agrees neither to dispense the study drug from, nor store it at any site other than the study site locations agreed upon with the sponsor. Study drug should be dispensed under the direction of the investigator.

Study drug will be supplied only to subjects participating in the study. Study drug may not be relabeled or reassigned for use to other subjects. The dispensation and use of study drug must be documented on the Drug Accountability Form. Used and unused study drug must be available for verification by the sponsor's site monitor during on-site monitoring visits. The destruction or return to the sponsor of used or unused study drug will be approved by the sponsor and documented on the Drug Return Form.

4 STUDY EVALUATIONS

4.1 Medical Questionnaires

Two questionnaires are provided - one designated for the mother and XLHED-affected neonate (Appendix 3) and one designated for male siblings of an enrolled neonate (Appendix 4). The former includes family history related to XLHED, pregnancy, labor and delivery, and neonatal data. The latter includes general medical history with an emphasis on issues common to XLHED-affected males. This questionnaire will be used for both affected and unaffected male siblings.

4.2 Pharmacodynamic/Efficacy Evaluations

Assessment of PD/efficacy endpoints will be performed on all subjects. The Sponsor will provide any equipment and training required for assessments.

4.2.1 *Growth and Development*

Cross-sectional data in patient populations with hypohidrotic ectodermal dysplasia consistently reports poor growth in infancy, most commonly poor weight gain and feeding issues, and an elevated risk of abnormal development (Clarke et al., 1987; Motil et al., 2005; Blüschke et al., 2010). The growth assessments will consist of feeding history as well as measurements of weight, length, and head circumference taken at study visits as part of the physical examination and plotted on standardized growth curves for males. The initial physical examination will include assessment of standard developmental milestones, and will be augmented at Months 2, 4 and 6 by a validated, standard of care infant assessment tool. Examples of such tools include but are not limited to the Bayley Scales of Infant Development II (BSID-II) and III (BSDI-III) and the Denver Development Screening Test II (DDST II) (Black and Matula, 2000). Whichever tool is selected should be designed for down to age 2 months of life and should be used for all follow-up visits.

4.2.2 *Thermoregulation*

XLHED-affected neonates and infants have a well-documented abnormality of thermoregulation (heat intolerance) and as a consequence are at elevated risk for life-threatening hyperthermia under unmonitored conditions (Clarke et al., 1987; Blüschke et al., 2010). At present there are no validated genetic, clinical or physiologic markers that identify the level of risk for a given XLHED-affected patient. In this protocol, assessment of thermoregulatory risk for an XLHED-affected neonate will provide valuable information for the family in preparing for a safe transition to home. Additionally, demonstration in the long-term extension study of an improved and sustained thermoregulatory improvement may be a key efficacy element in the response to study drug. Thus it is a relevant and appropriate

evaluation in this protocol to assess thermoregulation of study subjects under closely monitored conditions with direct physician observation.

Thermoregulation reflects both sweat and insensible losses from the respiratory tract, both organ systems with compromised function in XLHED (Chawla et al., 2008; Clarke et al., 1987; Zankl et al., 2001; Casal et al., 2007; Seeliger et al., 2005). For term newborns placed inside a heated isolette, there is a wealth of validated clinical data on how to perform thermoregulation studies safely and what are the normal response parameters (e.g. Hey, 1975; Sjors et al., 1997; Stothers and Wagner, 1984; Sulyok et al., 1976). Healthy term babies reach the point of having to sweat to maintain body temperature at an isolette temperature of approximately 34°C. For thermoregulation assessment the study subjects will be placed unbundled in an isolette at a starting temperature of no more than 33°C in the ICU with continuous vital sign monitoring including respiratory rate, heart rate and body temperature. Isolette temperature will be held at the starting temperature for 0.5 hours for initial adaptation and baseline vital signs, following which it will be raised stepwise by 1-1.5°C every 30 minutes until reaching 36.5°C to assess infant response (Rutter and Hull, 1979). Total observation time is anticipated to be no more than 3 hours.

Strict stopping criteria will be in effect including: (1) a body surface temperature of ≥37.9°C (Rutter and Hull, 1979); (2) a noticeable change in behavior, e.g. uncontrolled crying; or (3) a sustained heart rate or respiratory rate outside of the normal range (HR 120-160 per minute; respiratory rate 40-60 per minute; Cloherty et al. 2004). With any of these changes or at the discretion of the study physician monitoring the assessment, the subject will be removed from the isolette to an unheated observation table until all vital signs and physical examination return to Baseline. Additional interventions are not anticipated, but will be at the discretion of the monitoring physician and the ICU staff.

In this exploratory endpoint, each subject's pre-dosing response to this short and controlled environmental challenge will be compared with the published literature and with the result of thermoregulation assessment after EDI200 dosing. Additional assessments of thermoregulation and heat tolerance are not standardized for ages 2-6 months but will be included as efficacy endpoints in the long-term extension study.

4.2.3 *Eccrine Structures*

4.2.3.1 **Sweat Duct Density**

Sweat duct density (number/cm^2) from at least two different sites on the soles of the feet (newborns and infants) or palms (siblings age ≥1 year) will be determined through analysis of images collected by direct visualization with an approved device, the Lucid VivaScope 1500 (www.lucid-tech.com). This technology has been tested in controls and XLHED-affected males from the newborn period to adulthood without complication (Dietz et al., 2013; Huttner et al., 2012; ECP-005 Clinical Study

Report). An adhesive ring will be placed on the subject's palm/sole to which the VivaScope will be attached via a magnetic lock. A series of photographs will be taken of an area approximately 6mm X 6mm. An individual trained in the use of this device will be involved in the acquisition of all images.

Up to two independent image readers trained in the reading of VivaScope images will interpret the images and provide sweat duct counts for inclusion with the study data. If there is a discrepancy in their counts of 10% or greater on an individual image, then both readers will reinterpret the same image and a final assessment made as an average of the repeat sweat duct counts. To account for growth during the study, all sweat duct counts will be adjusted for body surface area (Haycock et al, 1978).

4.2.3.2 **Sweat Rate Testing**

Sweat rate assessment following cholinergic stimulation is a technique used commonly in clinical trials as reported for the evaluation of distinct conditions including orthostatic hypotension, diabetes, growth hormone deficiency, Parkinson's disease, hypohidrosis, and Fabry's disease (Itoh et al., 2003; Low et al., 1983; Ramaswami et al., 2007). Maximal sweating on the volar lower arm surface of each subject will be induced by pilocarpine iontophoresis followed by sweat collection using the Macroduct Sweat Collection System developed primarily for sweat collection and analysis in the diagnosis of Cystic Fibrosis from the newborn period on (www.wescor.com). The Collection System consists of the Webster Sweat Inducer, Pilogel® Iontophoretic Discs and Macroduct Sweat Collectors. The Macroduct Sweat Collection System is approved for subjects of all ages including neonates (Mastella et al., 2000) and the manufacturer provides adequate directions for the device's use.

Pilogel® Iontophoretic Discs are unique gel reservoirs of pilocarpinium ions that are simple and safe to use in the iontophoretic stimulation of sweat. A Pilogel® disc is inserted into each of the recessed stainless steel electrodes, which are then attached to the subject. The Webster Sweat Inducer is activated by a start switch subsequently delivering a safe and optimal quantity of pilocarpine for gland stimulation (equivalent to five minutes iontophoresis at 1.5 mA) followed by an automatic, programmed stop.

Following completion of the pilocarpine iontophoresis the Webster Sweat Inducer electrodes and discs are removed from the subject, the application site is wiped once with alcohol, and a Macroduct Sweat Collector is placed over the site of one electrode. The Macroduct Sweat Collector is held in place for approximately 30 minutes using a Velcro Macroduct Strap. Sweat volume is determined from microliter markings on a collection coil diagram.

Individuals trained in the use of the Macroduct Sweat Collection System will be involved in both procedures and the acquisition of the data. The manufacturer of the iontophoresis device does report the rare occurrence (1 in 50,000) of small skin burns at the site of application, and physicians will be available on site to evaluate any adverse event occurrence.

4.2.4 *Pulmonary Function Testing and eNO levels*

Pulmonary function testing will be performed in the sibling sub-study on all subjects age 5 years and older at a laboratory experienced with pediatric subjects. Additionally, levels of exhaled nitric oxide (eNO) as an indicator of pulmonary inflammation will be quantified non-invasively with an age-group appropriate device in all siblings age 4 years and older.

4.2.5 *Dry Eye Assessment*

The eye examination will be performed by an ophthalmologist experienced in assessments of tear film and ocular surface in infants as well as children and adults. In newborns and infants, the examination will document the presence/absence of signs of infection and irritation, as well as a tear film break-up time. For children 5 years or older (sibling sub-study) the assessment will also include the Shirmer test for rate of tear production and the OCULAR SURFACE DISEASE INDEX© questionnaire (Appendix 5).

4.2.6 *Skin Biopsy*

Three mm diameter punch biopsies of skin will be obtained from the upper outer thigh area. Sites will follow their institutions standard practice with regard to biopsy procedure. The biopsy site may require absorbable suture(s). RNA isolated from the skin biopsies will be assayed in expression analyses to establish a biochemical response to EDI200 treatment in these EDA-deficient subjects. Genes to be evaluated include but are not are not limited to those involved in the EDA/EDAR pathway, e.g. EDAR, CTGF (connective tissue growth factor), Shh (sonic hedgehog) and Lgr5 (leucine-rich G-protein coupled receptor). For each study subject, comparisons will be made between the expression profiles obtained at Baseline, after the first and the last dose of EDI200.

4.2.7 *Dental Imaging/Examination*

The absence of tooth buds is a key confirmatory finding in phenotype assessment of an XLHED-affected neonate and can be determined from a lateral radiograph (Swischuk, 2003). Radiation exposure will be minimized in this study with a single lateral film at Baseline. Follow-up radiographs will be included in the long-term extension study for PD/efficacy documentation (first follow-up expected at age 2 years). Radiographs are the preferred

imaging modality as they detect tooth bud mineralization but do not require sedation in the infant. At the discretion of the PI the procedure can be supplemented by an ultrasound.

The sibling sub-study includes a dental examination that is brief and age-appropriate involving an assessment of tooth count and tooth shape. No X-ray exposure will be involved.

4.3 Genetic Testing

To meet inclusion criteria for EDI200 administration, potential study subjects are required to have their XLHED diagnosis confirmed by genetic testing of the EDA gene and these test results relayed to the study site. EDA genetic testing itself is outside of the scope of this protocol. If requested, the families of prospective subjects in need of EDA genotyping will be referred to resources available to facilitate this testing. Consent from the family (written or verbal) will be obtained as part of the screening process to provide the study site with documentation of genetic testing results via a secure and confidential method including an option for electronic transmission.

It has been demonstrated that a polymorphism in the EDAR gene associated with increased activity may be associated with amelioration of some XLHED-symptoms (Cluzeau et al., 2012). As this has the potential to impact outcome measures, all participating neonates will be tested for this specific polymorphism, c.1540T>C, rs3827760, p.V370A. The testing may be performed on the prior DNA sample used for EDA genotype confirmation, although results are not required prior to the initiation of dosing.

4.4 Digital Facial Photographs

A facial recognition software algorithm is under development that will identify characteristics of XLHED-affected males as neonates, children and adults. The algorithm uses non-invasive 2D frontal photographs and will be used in this study to document the newborn facial appearance as well as changes in craniofacial appearance over time, including the long-term extension study. Facial frontal and lateral digital images will be obtained with a commercial camera, and all photographs will be anonymized prior to transmission for analysis to FDNA, the company developing the software algorithm (http://www.fdna.com).

4.5 Clinical and Safety Laboratory Evaluations

4.5.1 *Safety Laboratory Sampling*

Laboratory parameters measured at the study site will include a complete blood count (RBC, WBC, hemoglobin and hematocrit) with differential and platelet count, serum chemistries including glucose, electrolytes (Na, K, Cl, Ca), total protein and albumin, assessment of hepatic and renal function (BUN, serum creatinine, AST, ALT and alkaline phosphatase), and urinalysis (dipstick and microscopy). It will be the Principal Investigator's responsibility to assess laboratory parameters against local reference ranges and to assess the clinical significance of any out-of-range values.

4.5.2 *Pharmacokinetic Sampling*

Analysis will be performed to characterize EDI200 PK after the doses designated as dose #1 and #5. Blood samples (0.25 ml) for determination of EDI200 in plasma will be taken into collection tubes without additives on the days and times indicated. The model used to determine frequency of pharmacokinetic sampling incorporates a sparse sampling approach in order to reduce the number of blood samples required for each subject. Note that additional PK samples are scheduled for age 2 and 6 months to assess study drug persistence at low levels as was reported for XLHED adults.

PK samples will be drawn at approximately the following time points pre-dose (defined as prior to the start of infusion) and post-dose (defined as after infusion is completed):

	Pre-Dose	Post-Dose							
		15 (±5) min	3 (±.5) hrs	8 (±1) hrs	18 (±2) hrs	24(±2) hrs	48 (±4) hrs	168(±8) hrs	Age 2 months (±1 wk) & 6 months (±2 wks)
D0 (dose 1)	X	X	X	X		X	X		
D14 (dose 5)	X	X	X		X		X	X	X

Immediately upon sampling, the sample will be identified with a label bearing details of the study number, subject number, sampling time point, and a sample type. The sample will be separated by centrifugation at rotation 1500xg, 4°C for 10 minutes. Two 50 ul aliquots of serum will be transferred to polypropylene tubes labeled identically to the original blood sample and stored at approximately -70°C pending analysis. The time at which samples are taken, received into the separating room and placed in the freezer will be recorded in the study documentation.

4.5.3 *Immunogenicity Sampling*

Blood samples (~0.25 mL per sample) for immunogenicity sampling will be taken into serum separator tubes on the days indicated.

Immediately upon sampling, the sample will be identified with a label bearing details of the study number, subject number, sampling time point, and a sample type. The sample will be separated by centrifugation. Two equal aliquots of serum will be transferred to polypropylene tubes labeled identically to the original blood sample and stored at approximately -70°C pending analysis. The calendar date and 24-hour clock time at which samples are taken, centrifuged and placed in the freezer will be recorded in the study documentation.

4.5.4 *Total of Blood Volume*

The approximate number of safety laboratory evaluations and the approximate volume of blood that will be collected per subject throughout the study are as follows:

All Subjects	Genetic Testing (5 ml)*	Safety Labs (1.5 ml)	Immunogenicity (0.25 ml)	PK (0.25 ml)	Total Blood Volume (ml)	ml/kg (3.5 kg neonate)
Screening	0	0	0	0	0.00	
Baseline	1 x 5 = 5.0	1 x 1.5 = 1.5	1 x 0.25 = 0.25	0	6.75	1.93
Week 1	0	1 x 1.5 = 1.5	0	6 x 0.25 = 1.50	3.00	0.86
Week 2	0	0	0	0	0	0
Week 3	0	1 x 1.5 = 1.5	1 x 0.25 = 0.25	5 x 0.25 = 1.25	3.00	0.86
Week 4	0	1 x 1.5 = 1.5	0	1 x 0.25 = 0.25	1.75	0.50
Months 2,4,6	0	2 x 1.5 = 3.0	2 x 0.25 = 0.50	2 x 0.25 = 0.50	4.00	
Total	1 x 5 = 5.0	6 x 1.5 = 9.0	4 x 0.25 = 1.0	13 x 0.25 = 3.25	18.25	

* For testing of the EDAR polymorphism in the case that DNA is not available from prior genotyping

4.6 Safety Evaluations

The safety evaluations will consist of adverse events, concomitant medications, vital signs, weight, physical exam findings, and safety laboratory values. Adverse events will be recorded starting when the treatment Informed Consent document (ICF2) is signed and continuing until all study assessments are completed (including Month 6 follow-up evaluations for all AEs, and Month 6 + 28 days for SAEs). Information on the definition, characteristics, and reporting requirements are provided below.

4.6.1 *Adverse Events*

4.6.1.1 Definition

An adverse event (AE) is any reaction, side effect, or other untoward event (signs, symptoms, or changes in laboratory data) associated with participation in this study, whether or not the event is considered related to the study or any of the procedures being conducted. All AEs occurring after signing the informed consent document will be recorded. AEs will be ascertained on the basis of volunteered symptoms and clinical observation. AEs will be

recorded during the study on the appropriate CRF page. All AEs considered to be related to study procedures, and all serious adverse events (SAEs; see Section 4.5.2) will be followed until resolved or until a stable status has been achieved. SAEs will be recorded up to 28 days following the Day 168 visit.

4.6.1.2 Reporting Adverse Events

Any adverse event (AE, a clinical sign, symptom, or disease) temporally associated with this study, whether or not considered related to study drug, shall be documented on the case report form (CRF). All AEs reported by the subject or observed by the PI will be individually listed. The signs and symptoms, the date of onset, duration, relationship to study drug, action taken, and follow-up procedures will be reported.

4.6.1.3 Relationship

The relationship between an AE and the administration of study drug or the procedures employed in this study will be determined by the PI on the basis of his or her clinical judgment and the following definitions:

Definitely Related: Follows a reasonable temporal sequence from administration of study drug; follows a known response pattern to the study procedure; and, when appropriate to the protocol, is confirmed by improvement after stopping the study procedure (positive re-challenge) and by reappearance of the reaction after repeat exposure (positive re-challenge); and cannot be reasonably explained by known characteristics of the participant's clinical state or by other therapies.

Probably Related: Follows a reasonable temporal sequence from administration of study drug; follows a known response pattern to the study procedure; and, when appropriate to the protocol, is confirmed by improvement after de-challenge; and cannot be reasonably explained by the known characteristics of the participant's clinical state or by other therapies.

Possibly Related: Follows a reasonable temporal sequence from administration of study drug and follows a known response pattern to the study procedure but could have been produced by the participant's clinical state or by other therapies.

Unlikely Related: The reaction has little or no temporal sequence from administration of the study drug, and/or a more likely alternative etiology exists.

Not Related: Sufficient information exists to indicate that the etiology is unrelated to administration of study drug in this study. Two or more of the following variables apply:

- The AE does not follow a reasonable temporal sequence with occurrence of administration of study drug;

- The AE is readily explained by the participant's clinical state or other therapies.

4.6.1.4 Severity

The intensity of an AE, as determined by the PI, will be assessed and graded utilizing a 5-point scale according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v4.0). It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under section 4.6.2. If a subject experiences the same AE with more than one level of intensity, the highest level of intensity should be recorded on the CRF. The severity grading will be reported in the eCRF as follows:

Grade 1 = **Mild;** asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 = **Moderate**; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
Grade 3 = **Severe** or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
Grade 4 = **Life-threatening** consequences; urgent intervention indicated.
Grade 5 = **Death** related to AE.

4.6.1.5 Outcome

The outcome of an AE will be assessed as follows:

- Resolved
- Unresolved
- Resolved with sequelae
- Death
- Unknown

4.6.2 *Serious Adverse Event*

4.6.2.1 Serious Adverse Event Definition

An SAE is any AE that results in any of the following outcomes:

- Death
- A life threatening AE
  - The term "life-threatening" means that the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe
- An inpatient hospitalization or prolongation of existing hospitalization (24 hours or more)

- A persistent disability/incapacity, or a
- A congenital anomaly/birth defect
- Important medical event

An important medical event may not result in death, be life threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

4.6.2.2 Serious Adverse Event Reporting

The PI will report all SAEs to the Sponsor in a timely fashion, within 24 hours of awareness, by completing and faxing the SAE Report Form to CTI Safety as per directions described in the Study Reference Manual. The reporting PI is obligated to provide their initial assessment of the relationship between study drug and the occurrence of each SAE. Determination of expectedness and the reporting of the SAEs to relevant regulatory authorities will be determined by the Sponsor. The reporting PI is responsible for reporting all SAEs to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) as required by the appropriate regulations.

Based on the investigator's assessment of causality of the adverse event and discussions with the medical monitor, a decision will be made by the sponsor concerning the need for further action with respect to the future conduct of this trial. The primary consideration governing further action is whether new findings affect the safety of other subjects participating in the clinical study. If the discovery of a new adverse event related to study drug raises concerns over the safety of its continued administration to subjects, the sponsor or designee will take immediate steps to notify the Data Safety Monitoring Board (DSMB), the regulatory authorities and all the investigators participating in clinical studies of the study drug.

The Sponsor will notify the relevant regulatory authorities according to Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) regulations. The reporting PI will notify the Sponsor through the following contact:

Name:	CTI Global Drug Safety & Pharmacovigilance
Address:	10123 Alliance Road Cincinnati, OH 45242
Telephone:	1-877-755-0742
Fax:	1-866-215-5862
E-mail:	CTISafety@ctifacts.com

Additional SAE follow-up information, if required, should all be faxed to CTI Safety within 24 hours of receipt. The follow-up information should be documented on the original SAE Report Form following Good Documentation Practices and faxed with any additional relevant source

documentation. Additionally, the AE eCRF should be updated accordingly to match the SAE Report form.

SAE source documentation requested may include; discharge summary, diagnostic test results, consultation reports, relevant specimen cultures, diagnostics, or laboratory values. The investigator must ensure that all source documentation maintains each subject's anonymity. The site and subject number must be documented on every page, the subject's name replaced by the subject's study number, and all other protected health information should be redacted (e.g. social security number, medical record number, room number, etc.).

Compliance with the requirements for expedited reporting is essential. The sponsor or the sponsor's designee is responsible for informing the regulatory authorities as well as all other participating investigators of the following events:

- Any event associated with the use of the study drug, that is both serious and unexpected (SUSAR), or
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.

The sponsor or designee will expedite the reporting of all SUSARs to the appropriate regulatory authorities and the Institutional Review Board/Independent Ethics committee (IRB/IEC). The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse event (AE). For fatal or life threatening cases, the term will be a maximum of 7 calendar days for a preliminary report with another 8 calendar days for completion of the report. The sponsor or designee will also inform all investigators of such events.

The sponsor or designee will provide expedited reports of the following SUSARs to the IRB/IEC:

- SUSARs that have arisen in the clinical trial that were assessed by the EC
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that were assessed by the EC.

4.7 Concomitant Medication

There are no concomitant medications that are excluded from this study. There are no concomitant medications known to interact with EDI200.

4.8 Data Safety Monitoring Board (DSMB)

An independent DSMB will be established to monitor the safety of treated subjects. A European member has been added to the same DSMB in place for the Phase 1 adult safety

study (ECP-004) to monitor this neonate trial. All safety-related laboratory values will be available to the DSMB in real time. At the scheduled DSMB review meetings, detailed safety reviews will be provided to the DSMB including; adverse events, concomitant medications, infusion/injection site reactions, physical examination, weights and vital signs, and all PK and safety laboratory values. Scheduled DSMB meetings include the following:

- After dosing is completed in XLHED neonate cohort 1, the DSMB will meet and review safety and PK data from all cohort 1 subjects prior to initiation of dosing in XLHED neonate cohort 2. The timeframe for this review is approximately three weeks following dosing of the last cohort 1 subject. The cohort 1 PK data review is intended to confirm that the exposure levels in the cohort as a whole and for each subject were within the limits associated with safe study drug administration in the preclinical GLP toxicology studies, and that the expected exposure with dose escalation in cohort 2 will remain in the range that was safe and well tolerated. Additionally, the DSMB will review safety and PK data obtained from adult cohort 2 (NCT01564225, www.clinicaltrials.gov) dosed at the same 10 mg/kg/dose as is proposed for neonate cohort 2.
- At the end of the Study, DSMB will review and summarize all study safety data. DSMB summaries will be provided in a timely fashion to the Sponsor.

Unscheduled DSMB reviews will take place as outlined in Section 3.3.4-3.3.7 for single or accumulated adverse events. Additional safety-related evaluations of one or more subjects may be requested by the DSMB based on findings through the 6-month, end-of-study visit.

5 SCHEDULE OF STUDY ASSESSMENTS

5.1 Screening – End of first trimester through DOL #12

- Medical history related to XLHED in the family and for pregnancy, labor and delivery
- Verbal consent from both parents (if reasonably available) to provide documentation of genetic testing results to the study site by a secure and confidential method including the option for electronic transmission
- Inclusion/Exclusion criteria will be confirmed for parents and fetus/neonate

**A screening call may be conducted to assess eligibility for study participation, inclusion/ exclusion criteria, and availability of EDA genetic test results. If prior genotyping is not available, either cord blood or a neonatal blood sample may be sent to an accredited laboratory for testing.*

5.2 Baseline – DOL #2 through DOL #14

- Transport Informed Consent from both parents (if reasonably available) if neonatal transport to the study site is to be provided as part of the study
- Treatment Informed Consent from both parents (if reasonably available) for study procedures and study drug administration
- Confirmation of inclusion/exclusion criteria
- Updated medical history
- Full physical examination
- Blood draws for safety laboratories, EDAR gene V370A polymorphism testing, PK and immunogenicity
- Bioactivity assessments
    - Growth and development
    - Dental imaging
    - Digital facial photograph
    - Sweat duct density
    - Sweat rate
    - Dry eye assessment
    - Thermoregulation
    - Skin biopsy sample for molecular profiling
- Adverse Events & Concomitant Medications

5.3 Treatment

Day 0

- Brief physical exam (prior to dosing)
- Study drug administration (dose 1)
- Vital sign monitoring during and for 24 hours following study drug infusion
- Blood draw for PK analysis at the following timepoints:
    - Post-end of infusion timepoints: 15 min, 3 and 8 hours
- Adverse Events & Concomitant Medications

Day 1

- Brief physical exam
- Blood draw for safety laboratory evaluations
- Blood draw for PK analysis at the following timepoints:
    - 24 hours post dose 1
- Skin biopsy 24 hours post dose 1
- Adverse Events & Concomitant Medications

Day 2

- Blood draw for PK analysis at the following timepoints:
    - 48 hours post dose 1
- Adverse Events & Concomitant Medications

Day 4

- Brief physical exam (prior to dosing)
- Study drug administration (dose 2)
- Vital sign monitoring during and for 24 hours following study drug infusion
- Adverse Events & Concomitant Medications

Day 7

- Brief physical exam (prior to dosing)
- Study drug administration (dose 3)
- Vital sign monitoring during and for 24 hours following study drug infusion
- Adverse Events & Concomitant Medications

Day 11

- Brief physical exam (prior to dosing)
- Study drug administration (dose 4)
- Vital sign monitoring during and for 24 hours following study drug infusion
- Adverse Events & Concomitant Medications

Day 14

- Brief physical exam (prior to dosing)
- Study drug administration (dose 5)
- Vital sign monitoring during and for 24 hours following study drug infusion
- Blood draws for PK analysis at the following timepoints:
    - Pre-dose and the following post-end of infusion timepoints: 15 minutes, 3 and 18 hours
- Adverse Events & Concomitant Medications

Day 15

- Brief physical exam
- Skin biopsy for molecular profiling (24 hours after study drug administration)
- Adverse Events & Concomitant Medications

Day 16

- Blood draw for PK analysis at the following timepoints:
    - 48 hours post dose 5
- Blood draw for safety laboratory evaluations
- Blood draw for immunogenicity testing
- Adverse Events & Concomitant Medications

Day 21

- Full physical exam
- Blood draw for safety laboratory evaluations
- Blood draw for PK analysis at the following timepoints:
    - 168 hours post dose 5
- Thermoregulation assessment
- Adverse Events & Concomitant Medications

**If any visits are adjusted during the baseline and/or treatment portions of the study (if a subject is seen or dosed earlier or later than what is described in the protocol) then all subsequent visits (if applicable) should be adjusted accordingly.*

5.4 Post-Treatment

Follow-Up Visit 1 – Month of Life 2 (±1 week)

- Full physical exam
- Blood draw for safety laboratory evaluations
- Blood draw for immunogenicity testing
- Blood draw for PK
- PD/efficacy assessments
    - Growth and development

  - Sweat duct density
  - Sweat rate
  - Dry eye assessments
- Adverse Events & Concomitant Medications

Follow-Up Visit 2 – Month of Life 4 (±1 week)

- Full physical exam
- PD/efficacy assessments
  - Growth and development
- Adverse Events & Concomitant Medications

End-of-Study Visit – Month of Life 6 (±2 weeks)

- Full physical exam
- Blood draw for safety laboratory evaluations
- Blood draw for immunogenicity testing
- Blood draw for PK
- PD assessments
  - Growth and development
  - Digital facial photographs
  - Sweat duct density
  - Sweat rate
  - Dry eye assessments
- Adverse Events & Concomitant Medications

5.5 Unscheduled Visits

The Sponsor or DSMB may request unscheduled visits either during the subject's participation in the Study or after his completion. The unscheduled visits may include additional safety-related evaluations (including blood sampling) based on findings through the 6-month, end-of-study visit.

6 STATISTICAL METHODS

6.1 Sample Size

The sample size is based on clinical and practical considerations for a Phase 2 study in an ultra-rare genetic disorder with enrollment limited to newborns. It is considered to be appropriate to meet the objectives of the study while minimizing the exposure of volunteers. Each cohort is anticipated to enroll approximately 3-7 XLHED-affected neonates. No more than 10 subjects total will be enrolled.

6.2 Analysis Datasets

The safety analysis set will consist of all subjects who receive at least one dose of study medication. The PK analysis set will consist of those subjects who receive at least one dose of study medication and have sufficient concentration data to obtain a plasma concentration by time profile. The PD/efficacy analysis set will consist of all subjects who receive at least one dose of study medication and complete the follow-up assessments through at least month 2. No missing data will be replaced by values carried forward.

6.3 Primary and Pharmacodynamic/Efficacy Assessments

The safety assessment variables are AEs, concomitant medications, vital signs, weight, physical examination findings, hematology, clinical chemistry, and urinalysis laboratory test results.

The PK assessment variables will be the following derived PK parameters for EDI200:

- C_{max}, T_{max}, $AUC_{0\text{-}tau}$
- Other PK parameters including but not limited to clearance rate may also be examined.

The medical history and clinical evaluations for the sibling sub-study will be tabulated and intra-familial comparisons will be made with data obtained from the neonate subjects receiving study drug.

The following pharmacodynamic/efficacy outcomes will be monitored in all subjects receiving study drug:

- Growth and development
- Dentition (follow-up radiographs in extension study)
- Craniofacial development by digital photography
- Sweat duct density
- Sweat rate
- Dry eye signs and symptoms
- Thermoregulation
- Molecular expression profile of skin biopsy tissue

6.4 Pharmacodynamic/Efficacy Variables (not including sibling sub-study)

Growth and Development
Testing to be performed at Baseline, Months of Life 2, 4, 6:

- Weight, length, head circumference plotted on standardized growth curves for males
- Developmental assessments

Dental Imaging:
Testing to be performed at Baseline:

- Lateral jaw film

Craniofacial Development
Testing to be performed at Baseline, Month of Life 6

- Digital facial photographs

Sweat Duct Density
Testing to be performed at Baseline, Months of Life 2 and 6:

- Sweat ducts per 36 mm^2 on confocal microscopy image

Sweat Rate:
Testing to be performed at Baseline, Months of Life 2 and 6:

- Volume of induced sweat collected over 30 minutes following pilocarpine iontophoresis

Dry Eye Assessments:
Testing to be performed at Baseline, Months of Life 2 and 6:

- Examination for signs of infection and/or irritation, as well as tear film break-up time

Thermoregulation
Testing to be performed at Baseline, TD21:

- Clinical and vital sign response to isolette temperature range

Skin Biopsy for Molecular Expression Profile:
Testing to be performed at Baseline, TD1 (approximately 24 hours after 1st dose) and TD15 (approximately 24 hours after last dose):

- Analysis of gene expression on skin biopsy samples

6.5 Analysis of Safety and Pharmacokinetic Variables

Safety variables will be tabulated and presented for all subjects receiving one or more doses of EDI200. Change from Baseline over time will be presented by cohort for continuous variables including laboratory values and vital signs using descriptive statistics with n, mean, standard

deviation, minimum, median and maximum as appropriate. Shift tables will be presented. Out-of-range values will be flagged in the data listings and will also be presented separately.

AEs will be coded using the current MedDRA drug dictionary version. Only treatment emergent AEs will be included in the summary tables. The incidence of subjects reporting AEs will be summarized by system organ class, preferred term, severity and relationship to study drug.

The PK parameters of EDI200 will be listed and summarized by dosing cohort. Mean and individual plasma concentration-time curves will be presented on both linear and semi-logarithmic scales. The derivation of the PK variables from the EDI200 plasma concentrations will be determined using WinNonlin Professional v5.2, or higher. The PK parameters of EDI200 will be listed and summarized.

6.6 Statistical Methods

Individual subject values for EDA genotype and all endpoints, both at Baseline and across time, will be provided. Demographics for the entire study dataset will be presented using descriptive statistics. Table summaries of Baseline values for all endpoints will be provided for the following groups: all subjects and each dosing cohort. Descriptive statistics will be provided across time for each cohort with n, mean, standard deviation, minimum, median and maximum as appropriate.

6.7 Data Management

As outlined in section 7.5 the Sponsor or designee will forward questions regarding missing data or discrepancies to the PI.

The original terms used in the case report forms by the PI to identify adverse events will be coded according to the MedDRA dictionary. The percentage of subjects with adverse events will be tabulated overall and by the MedDRA body system and preferred term.

7 STUDY ADMINISTRATION

7.1 Protocol Modifications

Neither the PI nor Sponsor will modify this protocol without obtaining the concurrence of the other. All protocol amendments must be issued by the Sponsor, signed and dated by the PI, and should not be implemented without prior IRB/IEC approval, except where necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study (e.g., typographical errors, inconsistencies).

In situations requiring a departure from the protocol, the PI or other physician in attendance will discuss with the appropriate Sponsor representative. This contact will be made before implementing any departure from protocol. In all cases, contact with the Sponsor will be made as soon as possible in order to discuss the situation and agree on an appropriate course of action. Any departure from the protocol and the circumstances requiring it will be documented.

7.2 Monitoring

The Sponsor or their designee (hereby referred to as "Monitor") will monitor all aspects of the study as required by GCP and any existing standard operating procedures for compliance with applicable regulations. These individuals will have access to all records necessary to ensure integrity of the data and will review progress of the study with the PI.

The monitor will compare the data entered into the CRF's with any source documents. The nature and location of any source documents will be identified in advance. This will ensure that all sources of original data required to complete the CRF are known to the Sponsor and investigational staff; and are accessible for verification by the Monitor. If electronic records are maintained, the method of verification must be discussed with the investigational staff. At a minimum, source documentation must be available to substantiate subject identification, eligibility and participation, proper informed consent procedures, adherence to protocol procedures, record of safety parameters, adequate reporting and follow-up of adverse events, completion and reason of withdrawal/ termination. Specific items required as source documents will be reviewed with the PI before the study. The author of an entry in the source documents will be identifiable.

If any data are recorded directly into the CRF, at a minimum there should be an entry in the source document that each of the assessments was done, and by whom and the date it was done. The author of an entry in the source documents must be identifiable. The CRF data will be entered into an appropriate data storage system and verified for accuracy.

Direct access to source documentation must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. Findings from this review

of CRF's and source documents will be discussed with the investigational staff. The Sponsor expects that, during monitoring visit(s), the relevant investigational staff will be available, the source documentation will be available, and a suitable environment will be provided for review of study-related documents. The monitor will provide feedback on the study conduct to the PI.

The investigator will permit trial-related monitoring, audits, audits, IRB/IEC review, and regulatory inspection(s), and providing direct access to source data/documents.

7.3 Ethic Aspects

7.3.1 PI Responsibilities

The PI is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines, Good Clinical Practice (GCP), and applicable regulatory requirements.

GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well being of study subjects are protected, consistent with the principles that have originated in the Declaration of Helsinki and that the clinical study data are credible.

7.3.2 Institutional Review Board/Independent Ethics Committee

The PI will provide the Institutional Review Board/Independent Ethics committee (IRB/IEC) with all requisite material, including a copy of the protocol, informed consent and all subject materials. The study will not be initiated until the IRB/IEC provides written approval of the protocol and the informed consent and the PI has obtained documents approved by the IRB/IEC. Any reports requested on the progress of this study by the PI will be made to the IRB/IEC and the Sponsor.

7.3.3 Informed Consent

A properly executed, written informed consent in compliance with national and local regulations and GCP guidelines will be obtained from each subject prior to entering the study or performing any study-related procedure.

The PI will submit a copy of the informed consent document to the IRB/EC for review and approval before research subjects are enrolled. The PI will provide a version of the signed informed consent to the subject and a signed version will be maintained in the subject's research record.

7.3.4 Confidentiality of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the safety, quality, and utility of the procedures performed during this study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

The Sponsor ensures that the personal data are:

- Processed fairly and lawfully
- Collected for specified, explicit, and legitimate purposes and not further processed in a way incompatible with these purposes
- Adequate, relevant, and not excessive in relation to said purposes
- Accurate and, where necessary, kept up to date

Explicit consent for the processing of personal data will be obtained from the participating subject before collection of data. Such consent should also address the transfer of the data to other entities and to other countries, if applicable.

The subject has the right to request through the PI access to his/her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps should be taken to respond to such request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel and designees whose responsibilities require access to personal data agree to keep the identity of study subjects confidential.

7.4 Subject Identification Register

The PI agrees to complete a subject identification register to permit easy identification of each subject during and after the study. The Monitor will review the document for completeness.

The subject identification register will be treated as confidential and will be filed by the PI in the Regulatory Binder. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by initials and assigned number only.

7.5 Case Report Form Completion

All of the clinical data will be captured via electronic data capture (EDC) using an approved and validated EDC system. The investigator site staff will enter and edit the data via a secure network, with secure access features (username, password and secure identification – an electronic password system). A complete electronic audit trail will be maintained.

The investigator will approve the data using an electronic signature, and this approval is used to confirm the accuracy of the data recorded (CFR 21, Part. 11, 2011).

Electronic CRF's (eCRF) will be used for all patients. The investigator's data will be accessible from the investigator's site throughout the trial. The eCRFs must be kept current to reflect patient status at each phase during the course of the trial. The patients must not be identified on the eCRF by name. The appropriate coded identification (i.e. Patient Number) must be used. The investigator must make a separate confidential record of these details (subject identification record) to permit identification of all patients enrolled in a clinical trial in case follow-up is required.

Copies of the eCRF together with all data changes made will be supplied to the investigator at the end of the trial. The investigator will be responsible for retaining all records pertaining to the trial as specified in the appropriate contract.

7.6 Data Quality Assurance

Steps to be taken to assure the accuracy and reliability of data include the selection of a qualified PI, review of protocol procedures with the PI and associated personnel before the study, and a monitoring visit(s) by the Sponsor. Instruction for completion of CRFs will be provided and reviewed with study personnel before the start of the study. The Monitor will review CRFs for accuracy and completeness during the conference and/or during a monitoring visit(s). Any discrepancies will be resolved with the PI or designee, as appropriate. The data will be entered into an appropriate data storage system and verified for accuracy.

7.7 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

APPENDIX 1 – AUTOMATIC PHENOTYPE IDENTIFICATION OF XLHED PATIENTS

FINAL REPORT

Provided as a separate document.

APPENDIX 2 – THE NATIONAL CANCER INSTITUTE (NCI) COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS V4.0 (CTCAE)

VERSION 4.0

US DEPARTMENT OF HEALTH AND HUMAN SERVICES- NATIONAL INSTITUTES OF HEALTH-NATIONAL CANCER INSTITUTE

Provided as a separate document.

APPENDIX 3 – MEDICAL QUESTIONNAIRE FOR MOTHERS AND XLHED-AFFECTED NEONATES

Medical Questionnaire for Mothers and XLHED-Affected Neonates

Participant's Initials: ☐☐☐ **Can be left blank if choice of name is not yet finalized*

Today's Date: ☐☐/☐☐/☐☐☐☐

Date of birth: ☐☐/☐☐/☐☐☐☐
DD/MM/YYYY

Has the mother been diagnosed with HED? ☐Yes ☐No

If yes, age at diagnosis: ☐0-5 years ☐6-17 years ☐≥18 years

Does the mother have any family members diagnosed with HED? ☐Yes ☐No

If yes, check all that apply:
☐Mother
☐Father
☐Sisters
☐Brothers
☐Aunts
☐Uncles
☐Other

If other, specify:

Has the mother or any family member(s) had genetic testing for HED? ☐Yes ☐No

**Every attempt should be made to obtain a copy of the genetic test results. The results must be provided to the study site and will also be provided to the lab conducting your baby's genetic testing in order to expedite the testing process.*

Mother's age at delivery: ☐☐

What number pregnancy is/was this child for the mother? ☐☐

Is the mother currently pregnant? ☐Yes ☐No

Thinking of *all* of the mother's pregnancies to date, including this one, how many resulted in each of the following:

	Number
Miscarriage in the first trimester (up to 14th week of pregnancy)	☐☐
Miscarriage later in pregnancy	☐☐
Stillbirth	☐☐
Preterm birth (prior to 37 weeks)	☐☐
Full term birth (37 weeks or more)	☐☐

Did the mother have any of the following complication during ***this child's*** (the study subject) pregnancy? ☐Yes ☐No

If yes, please list treatment.

Diabetes: _____
High blood pressure: _____
Infections, fevers and illnesses: _____
Other problems/complications: _____

Medications used during pregnancy: _____
_____

Are any of these medications investigational? ☐Yes ☐No

Did the mother have any of the following?
☐Ultrasound
☐1st trimester screen/triple/quad screen
☐Amniocentesis or CVS

Were any results from this testing abnormal? ☐Yes ☐No

If yes, please explain:
_____
_____

Check here ☐ if your child is not born yet and do NOT complete the rest of this form.

The child was born:
☐Full-term
☐Prematurely (weeks premature: ☐☐)

If premature, please list the reason:
_____

The child was born: ☐Vaginally ☐By C-section
If by C-section, why: _____

Birth Hospital: _____

Birth location:

Country: _____
City: _____
State (if applicable): _____

Birth weight: ☐☐.☐ kg
Birth Length: ☐☐.☐ cm
Birth head circumference: ☐☐.☐ cm

Did your child have any problems after delivery or require admission to the Neonatal Intensive Care Unit (NICU)? ☐Yes ☐No

If yes, please explain:

_____

_____

Did he/she pass the:
Newborn metabolic screen: ☐Yes ☐No ☐Unsure
Newborn hearing screen: ☐Yes ☐No ☐Unsure

How many days old was child when he/she went home from the hospital? ☐☐

Did the child have any other problems in the first few days of life? ☐Yes ☐No
If yes, please explain: _____

_____

APPENDIX 4 – MEDICAL QUESTIONNAIRE FOR MALE SIBLINGS OF STUDY SUBJECTS

Medical Questionnaire for Male Siblings of Study Subjects

*One questionnaire to be completed by each male sibling

Participant's Initials: ☐☐☐

Participant's ID #: ☐☐☐
*To be completed by study personnel

Gender: ☐Male

Today's Date: ☐☐/☐☐/☐☐☐☐

Date of birth: ☐☐/☐☐/☐☐☐☐
DD/MM/YYYY

Are you currently experiencing any major medical problems that would prevent you from participating in this study? ☐Yes ☐No

Do you have a known hypersensitivity to pilocarpine or pilocarpine-like muscarinic agonists (Examples: Urecholine, Salagen, Pilocar, and Provocholine)? ☐Yes ☐No

Do you have a pacemaker? ☐Yes ☐No

Have you been diagnosed with HED? ☐Yes ☐No

If yes, age at diagnosis: ☐0-5 years ☐6-17 years ☐≥18 years

Do you have any family members diagnosed with HED? ☐Yes ☐No

If yes, check all that apply:
☐Mother ☐Father ☐Sisters ☐Brothers ☐Aunts ☐Uncles ☐Other
If other, specify:

Have you or any family member(s) had genetic testing for HED? ☐Yes ☐No

Do you know the genetic test results? ☐Yes ☐No

Have you ever been referred to any of the following types of physicians?

Dermatologist	☐Yes	☐No
Pediatric dermatologist	☐Yes	☐No
Geneticist	☐Yes	☐No
Genetic counselor	☐Yes	☐No
Dentist	☐Yes	☐No
Pediatric dentist	☐Yes	☐No

Do you have decreased sweating?		☐Yes ☐No
Do you sweat on certain parts of your body?		☐Yes ☐No
If so, from what body part(s) do you sweat and at what age did you notice you started sweating in that area?		
Body Part: ______	Age you noticed:	☐0-5 yrs ☐11-17 yrs ☐6-10 yrs ☐≥18 yrs
Body Part: ______	Age you noticed:	☐0-5 yrs ☐11-17 yrs ☐6-10 yrs ☐≥18 yrs
Body Part: ______	Age you noticed:	☐0-5 yrs ☐11-17 yrs ☐6-10 yrs ☐≥18 yrs
Body Part: ______	Age you noticed:	☐0-5 yrs ☐11-17 yrs ☐6-10 yrs ☐≥18 yrs
Body Part: ______	Age you noticed:	☐0-5 yrs ☐11-17 yrs ☐6-10 yrs ☐≥18 yrs
Body Part: ______	Age you noticed:	☐0-5 yrs ☐11-17 yrs ☐6-10 yrs ☐≥18 yrs
Do you have unexplained fevers?		☐Yes ☐No
Did you ever suffer from seizures associated with fever?		☐Yes ☐No
Do you suffer from heat intolerance?		☐Yes ☐No
Is your exercising limited by heat intolerance?		☐Yes ☐No

Does your decreased sweating/heat intolerance affect your: *Check all that apply*	☐Daily life ☐Choice of occupation ☐Involvement in indoor sports ☐Involvement in outdoor sports ☐Decision to live in cooler climate ☐Choice of vacation destinations ☐Ability to travel

Have you experienced hair or eyebrow thinning or scalp hair loss?	☐Yes ☐No
If yes, what age were you when you noticed the loss of hair?	☐0-5 yrs ☐6-10 yrs ☐11-17 yrs ☐≥18 yrs
How often do you get your hair cut?	☐Daily ☐Weekly ☐Monthly ☐Yearly
Do you get haircuts less often than unaffected siblings/ classmates?	☐Yes ☐No
Have you ever tried a topical treatment to reduce hair thinning?	☐Yes ☐No

Do you have problems with your teeth (no teeth, missing or misshapen teeth)?		☐Yes	☐No
		Dentures	Implants
If yes, describe age of treatment with dentures and/or implants if applicable (check all that apply):	1-5 years	☐	☐
	6-10 years	☐	☐
	11-17 years	☐	☐
	≥18 years	☐	☐
To the best of your knowledge how many baby teeth did you develop?		☐☐	
To the best of your knowledge how many adult teeth did you develop?		☐☐	
Do you suffer from dry mouth?		☐Yes	☐No
Do you suffer from dry eyes?		☐Yes	☐No
Do you require eye drops on a regular basis?		☐Yes	☐No
Do you suffer from frequent eye infections?		☐Yes	☐No

Did you have chronic nasal drainage/blockage as a child?			☐Yes	☐No
Did you suffer from nosebleeds as a child?			☐Yes	☐No
If yes, at what age did you first notice them?	☐0-5 yrs	☐11-17 yrs		
	☐6-10 yrs	☐≥18 yrs		
Do you still experience nosebleeds?			☐Yes	☐No
How many times per year do you have nosebleeds?	☐☐			
Did you have respiratory related problems as a child?			☐Yes	☐No
If yes, were you ever hospitalized for antibiotic therapy?			☐Yes	☐No
Do you suffer from sinus infections most years?			☐Yes	☐No
If so, at what age did these sinus infections start?	☐0-5 yrs	☐11-17 yrs		
	☐6-10 yrs	☐≥18 yrs		
Do you suffer from asthma?			☐Yes	☐No
If so, do you require medication to manage your asthma?			☐Yes	☐No
Do you experience a hoarseness of your voice?			☐Yes	☐No
If yes, at what age did you first notice it?			☐Yes	☐No
Is the hoarseness worse during the cold months?			☐Yes	☐No

Do you have problems with dry skin?	☐Yes	☐No
Have you ever had a diagnosis of eczema or atopic dermatitis?	☐Yes	☐No
If yes, have you tried prescription medications?	☐Yes	☐No

If yes, list medications:

Do you have a family history of eczema (other than XLHED males)? ☐Yes ☐No

Hypohidrosis Severity 5-Point Likert Scale				
1	**2**	**3**	**4**	**5**
Sweat as much as people without ED	Sweat a little less than people without ED (no problems in hot weather)	Some problems in sweating (sometimes have problems in hot weather)	A little sweating (I have problems in hot weather	No sweating at all (I have problems in hot weather)

Alopecia (hair loss or thinning) Severity 5-Point Likert Scale				
1	**2**	**3**	**4**	**5**
Normal hair	Mild (<25%) hair loss	Moderate (25-75%) hair loss	Severe (>75%) hair loss	No hair

APPENDIX 5 – OCULAR SURFACE DISEASE INDEX© (OSDI©)

Provided as a separate document.

REFERENCES

Black, MM, Matula K. 2000. *Essentials of Bayley Scales of Infant Development-II Assessment.* New York, J Wiley & Sons, Inc.

Blüschke G, Nusken KD, Schneider H. 2010. Prevalence and prevention of severe complications of hypohidrotic ectodermal dysplasia in infancy. *Am J Med Gen A*. 86: 397-9.

Casal M, Lewis J, Mauldin E, Tardivel A, Ingold K, Favre M, Paradies F, Demotz S, Gaide O, Schneider P. 2007. Significant Correction of Disease after Postnatal Administration of Recombinant Ectodysplasin A in Canine X-Linked Ectodermal Dysplasia. *Am J Hum Genet*. 81: 1050-1056.

Chawla, D, Agarwal R, Deorari A, Paul, V. 2008. Fluid and electrolyte management in term and preterm neonates. NICU Protocol. Division of Neonatology, Department of Pediatrics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi.

Clarke A, Sarfarazi M, Thomas NS, Roberts K, Harper PS. 1987. X-linked hypohidrotic ectodermal dysplasia: DNA probe linkage analysis and gene localization. *Hum Genet.* 75(4): 378-80.

Cloherty JP, Eichenwald EC, Stark AR. 2004. Manual of Neonatal Care (Fifth Ed). Philadelphia, PA: Lippincott, Williams & Wilkins.

Cluzeau C, Hadj-Rabia S, Bal E, Clauss F, Munnich A, Bodemer C, Headon D, Smahi A. 2012. The EDAR370A allele attenuates the severity of hypohidrotic ectodermal dysplasia caused by EDA gene mutation. *Br J Dermatol* 166:678-81.

Dietz J, Kaercher T, Schneider AT, Zimmerman T, Huttner K, Johnson R, Schneider H. 2013 Apr 4. Early respiratory and ocular involvement in X-linked hypohidrotic ectodermal dysplasia. *Eur J Pediatr* Epub ahead of print.

Ectodysplasin A (Fc:EDA1 aka EDI200) Replacement Therapy In A Canine Model Of Ectodermal Dysplasia: Pharmacological Assessment (NCD-200-11-005). Edimer Pharmaceuticals, Inc.

EDI200: A 3-Week Intraperitoneal/Intravenous Toxicity Study in Juvenile Dogs with a 2-Week Recovery Period (1800-010). Edimer Pharmaceuticals, Inc.

EDI200: A 3-Week Intraperitoneal Toxicity Study in Juvenile Mice with a 2-Week Recovery Period (1800-009). Edimer Pharmaceuticals, Inc.

"Electronic Records: Electronic Signatures." *Code of Federal Regulations* Title 21, Pt. 11, 2011 ed.

Gaide O, Schneider P. 2003. Permanent Correction of an Inherited Ectodermal Dysplasia with Recombinant EDA. *Nat Med*. 9: 614-618.

Haycock, G. B., Schwartz, G. J., & Wisotsky, D. H. 1978. Geometric method for measuring body surface area: a height-weight formula validated in infants, children, and adults. *J Pediatr*. 93(1), 62-6.

Hey E. 1975. Thermal neutrality. *British Med Bull. 31*(1): 69-74.

Huttner K, Grange D, Klein O, Schneider H. 2012, February. Genotype/phenotype correlations in XLHED: Insights into the biology of ectodysplasin. Poster session presented at the 2012 Dermatogenetics Conference. Miami, Florida.

Itoh H, Uebori S, Asai M, Kashiwaya T, Atoh K, Makino I. 2003. Early Detection of Orthostatic Hypotension by Quantitative Sudomotor Axon Reflex Test (QSART) in Type 2 Diabetic Patients. *Internal Med*. 42: 560-564.

Low P, Caskey P, Tuck R, Fealey R, Dyck P. 1983. Quantitative Sudomotor Axon Reflex Test in Normal and Neuropathic Subjects. *Ann Neurol*. 14: 573-580.

Mastella G, Di Cesare G, Borruso A, Menin L, Zanolla L. 2000. Reliability of sweat testing by the Macroduct collection method combined with conductivity analysis in comparison with the classic Gibson and Cooke technique. *Acta Paediatrica. 89*(8): 933-7.

Mauldin E, Gaide O, Schneider P, Casal M. 2009. Neonatal Treatment with Recombinant Ectodysplasin Prevents Respiratory Disease in Dogs with X-Linked Ectodermal Dysplasia. *Am J Med Genet A.* 149A: 2045-2049.

Miller, R. 2003. Marginal Transfer of ReoPro™ (Abciximab) Compared with Immunoglobulin G (F105), Inulin and Water in the Perfused Human Placenta In Vitro. *Placenta. 24*(7): 727-738.

Motil KJ, Fete TJ, Fraley JK, Schultz RJ, Foy TM, Ochs U, et al. 2005. Growth Characteristics Of Children With Ectodermal Dysplasia Syndromes. *Pediatrics*. 116(2): 229-34.

Ramaswami U, Wendt S, Pintos-Morell G, Parini R, Whybra C, Leon Leal J, Santus F, Beck M. 2007. Enzyme Replacement Therapy with Agalsidase Alfa in Children with Fabry Disease. *Acta Paediatr*. 96: 122-127.

Rutter N, Hull D. 1979. Response of term babies to a warm environment. *Arch Dis Child. 54*(3): 178-183.

Seeliger F, Drögemüller C, Tegtmeier P, Baumgärtner W, Distl O, & Leeb T. 2005. Ectodysplasin-1 deficiency in a German Holstein bull associated with loss of respiratory mucous glands and chronic rhinotracheitis. *J Comp Pathol*. 132(4): 346-9.

Sjörs G, Hammarlund K, Sedin, G. 1997. Thermal balance in term and preterm newborn infants nursed in an incubator equipped with a radiant heat source. *Acta Paediatrica. 86*(4): 403-9.

Stothers J K, Warner R M. 1984. Thermal balance and sleep state in the newborn. *Early Hum Dev*. *9*(4): 313-22.

Sulyok E, Jequier E, Prod'hom L. 1976. Relationship between body size, thermal balance and thermal insulation of term infants under various ambient conditions. *Biol Neonate*. *28*: 42-56.

Sweat Duct Imaging in Mother/Newborn Dyads (ECP-005). Clinical Study Report. Edimer Pharmaceuticals, Inc.

Swischuk, L. 2003. Imaging of the Newborn, Infant and Young Child (Fifth). Philadelphia, PA: Lippincott, Williams and Wilkins.

The Effect of Ectodysplasin A (Fc: EDA1) Replacement Therapy in a Canine Model of Ectodermal Dysplasia (NCD-22-11-004). Edimer Pharmaceuticals, Inc.

Ulm M R, Kratochwil A, Ulm B, Solar P, Aro G, Bernaschek, G. 1998. Three-dimensional ultrasound evaluation of fetal tooth germs. *Ultrasound Obst Gyn*. *12*(4): 240-3.

Zankl A, Addor M, Cousin P, Gaide A, Gudinchet F, Schorderet D. 2001. Fatal outcome in a female monozygotic twin with X-linked hypohidrotic ectodermal dysplasia (XLHED) due to a de novo t(X;9) translocation with probable disruption of the EDA gene. *Eur J Pediatr*. 160: 296-99.

Protocol Version 4 (Germany Only)
16 Jul 2014

Clinical Protocol

A Phase 2 open-label, dose-escalation study to evaluate the safety, pharmacokinetics, immunogenicity and pharmacodynamics/efficacy of EDI200, an EDA-A1 replacement protein, administered to infants with X-Linked Hypohidrotic Ectodermal Dysplasia (XLHED)

Protocol: ECP-002

Investigational Product: EDI200

Sponsor:

Edimer Pharmaceuticals, Inc.
55 Cambridge Parkway
Suite 102W
Cambridge MA 02142

IND Number: 109262
EudraCT Number: 2012-003561-17

Issue Date: 16JUL2014
Version: 4

TABLE OF CONTENTS

PROTOCOL AMENDMENTS

Previous Versions
19FEB2013, original
02APR2013, version 2*
24JUN2013, version 3
*Version 2 was issued prior to the enrollment of subjects and included only minor changes for clarification

Amendment #/Date	Applicable Section	Original Text	New/Revised Text/Description	Rationale
4 24JUL2014	Protocol Amendments	Version dated 12JUN2013	Version dated 24JUN1013	Correct date of version 3 is 24JUN2013
4 24JUL2014	Cover Page, Executive Summary, Synopsis, Time and Events Schedule, 1.1, 2.2, 3.1, 3.2, 3.3, 4.1, 4.2, 4.4, 5.2, 5.3, 5.4, 5.5, 6.3, 6.4, 6.5, Appendix 4, References	See 24JUN2013 protocol version 3	Several minor changes made to allow for female study subjects	Inclusion of female newborns based on: (1) newly published data reporting an increased risk for XLHED-affected females in abnormalities of growth, respiratory infections, dentition, eczema and dry eyes; (2) preclinical data on abnormal mammary gland development in XLHED; and (3) both the Phase 1 adult safety study and all IND-enabling toxicology studies were conducted in males and females with no gender-associated safety findings.
4 24JUL2014	Time and Events Schedule, 3.1.6, 5.4	Previous protocol versions included males only	Several minor changes made to remove sweat duct density and dry eye assessment from the 2	Data from the first four subjects does not support

			month follow up visit.	conducing these procedures at month 2.
4 24JUL2014	References	Blüschke G, Nusken KD, Schneider H. 2010. Prevalence and prevention of severe complications of hypohidrotic ectodermal dysplasia in infancy. Am J Med Gen A. 86: 397-9.	Blüschke G, Nusken KD, Schneider H. 2010. Prevalence and prevention of severe complications of hypohidrotic ectodermal dysplasia in infancy. Early Hum Dev. 86: 397-9.	Correction to journal name
3 24JUN2013	Cover Page, Synopsis	A Phase 2 open-label, dose-escalation study to evaluate the safety, pharmacokinetics and pharmacodynamics/efficacy of EDI200, an EDA-A1 replacement protein, administered to male infants with X-Linked Hypohidrotic Ectodermal Dysplasia (XLHED)	A Phase 2 open-label, dose-escalation study to evaluate the safety, pharmacokinetics, immunogenicity and pharmacodynamics/efficacy of EDI200, an EDA-A1 replacement protein, administered to male infants with X-Linked Hypohidrotic Ectodermal Dysplasia (XLHED)	Immunogenicity added to study title
3 24JUN2013	Executive Summary	See 02APR2013 protocol version 2	Several minor changes made to Executive Summary	Clarification
3 24JUN2013	Time and Events Schedule	Change made to biopsy and PK sample schedule	Biopsy removed from Month 6 visit, PK sample removed from Day 15 visit	Correction and clarification
3 24JUN2013	Time and Events Schedule	Change made to PK sample schedule	PK sample added to baseline and month 6	Modification of PK sample schedule (similar minor changes made throughout protocol)
3 24JUN2013	Time and Events Schedule	Change made to safety labs and immunogenicity sample schedule	Safety labs and immunogenicity sample moved from day 15 to day 16	Modification of safety labs and immunogenicity sample schedule (similar minor changes made throughout protocol)
3 24JUN2013	Time and Events Schedule	A full physical exam will be conducted at baseline, treatment days 7 and 14 and at the months 2, 4 and 6 follow-up visits. The full physical exam will include weight, height, head	A full physical examination will be conducted at baseline, day 21, months 2, 4, and 6. With the full physical examination will be the following quantitative assessments; weight,	Clarification on components of brief and full physical exam

		circumference and vital signs. A brief physical exam will be conducted at treatment days 0, 1, 4, 11, 15 and 21. The brief physical exam will include vital signs. On dosing days vital signs will also be collected every 4 hours following the end of the infusion for 24 hours.	height, head circumference and vital signs (temperature, blood pressure, heart rate and respiratory rate). A brief physical examination will be conducted at treatment days 0, 1, 4, 7, 11, 14 and 15. The brief physical examination will include overall appearance (normal or abnormal and if abnormal why), skin appearance, cardiovascular, pulmonary and abdominal evaluation. With the brief physical examination will be weight and a set of vital signs (temperature, blood pressure, heart rate and respiratory rate). On dosing days vital signs will also be collected pre- and post dosing as described in section 3.3.8.	
3 24JUN2013	Time and Events Schedule, 4.5.2	New text added	Time windows added for acceptable sampling	Provision for obtaining samples outside of specified time points
3 24JUN2013	Time and Events Schedule	Subjects may provide dental X-rays from an outside source. No dental radiographs will be obtained at the study site.	No dental radiographs will be taken as part of this sibling sub-study. Subjects will be asked to provide copies of recent dental X-rays from an outside source.	Clarification that no dental radiographs are done as part of the sibling sub-study (similar minor changes made throughout protocol)
3 24JUN2013	Time and Events Schedule	See 02APR2013, protocol version 2	Several minor changes made to Time and Events Schedule	Clarification
3 24JUN2013	1.1	See 02APR2013, protocol version 2	Several minor changes made	Clarification
3 24JUN2013	3	See 02APR2013, protocol version 2	Several minor changes made	Clarification
3 24JUN2013	3.1.5	The schedule of events for the In-Clinical portion of the study is presented in the Time and Events Table. In each cohort the first subject	The subject will be admitted to the study site during the entire dosing period. The schedule of events for this portion of	Clarification of dosing stratification

		enrolled will complete dosing of study medication, and if no significant AEs are observed then the remaining cohort subjects may begin dosing one week later. Subjects will have vital sign monitoring during and for 24 hours following each dose of study drug. The Medical Monitor and study PI will be responsible for evaluation of all AE and safety laboratory results.	the study is presented in the Time and Events Table. In each cohort, the first subject enrolled will complete the 15-day dosing period and undergo monitoring for an additional week at the study site. The site and Sponsor Medical Monitors will then review all AE and safety laboratory data. In the absence of any clinically significant AE's the remaining cohort subjects may begin dosing. It is anticipated that the timeframe from last dose of the first cohort subject through AE review will be approximately 2 weeks.	
3 24JUN2013	3.3.4, 3.3.6, 3.3.7	FDA	National Competent Authorities	Term FDA replaced with National Competent Authorities
3 24JUN2013	3.3.8	EDI200 will be thawed to room temperature on the day of dose administration, pooled in syringe(s) and infused via a syringe pump infusion system. The study drug shall be infused routinely over a period of 2 hours, but not to exceed 5 ml/kg/hr or 500 mg EDI200/hr.	EDI200 will be thawed to room temperature on the day of dosing, pooled in syringe(s) and administered via a syringe pump infusion system. The study drug shall be administered by slow IV infusion over at least 30 min, not to exceed 5 ml/kg/hour or 8.5 mg/min EDI200, in order to minimize the risk of infusion-related AE (refer to Investigational Brochure, Section 6.2). For more information on the preparation of EDI200 see the Pharmacy/Investigator Manual.	Clarification of infusion procedure
3 24JUN2013	3.3.8	New text added	During study drug administration and for 24 hrs following infusion the subject will have continuous heart rate and respiratory rate monitoring. A full set of vital signs	Clarification of continuous monitoring (similar minor changes made throughout protocol)

			including temperature, blood pressure, heart rate and respiratory rate will be documented on the following schedule: • Pre dosing - a single set of vital signs within 1 hour of initiating dose infusion • Post dosing: o 15 min after end of infusion, o 1 hr and 4 hrs after end of infusion, o then q4 hrs up to 24 hrs after end of infusion If the unit in which the subject is receiving study drug requires additional monitoring, then that data will be added to the subject's record.	
3 24JUN2013	3.3.8	New text added	The intravenous site will be assessed for patency and signs of local irritation prior to the start of the infusion, every 30 minutes during infusion, and at the end of study drug infusion.	Clarification of infusion site monitoring
3 24JUN2013	4.2.1	The initial physical examination will include assessment of standard developmental milestones, and will be augmented at Months 2, 4 and 6 by the Bayley Scales of Infant Development II (BSID-II), a well-validated assessment tool for use at 1-42 months of age (Black and Matula, 2000).	The initial physical examination will include assessment of standard developmental milestones, and will be augmented at Months 2, 4 and 6 by a validated, standard of care infant assessment tool. Examples of such tools include but are not limited to the Bayley Scales of Infant Development II (BSID-II) and III (BSDI-III) and the Denver Development Screening Test II (DDST II) (Black and Matula, 2000). Whichever tool is selected should be designed for ages down to	Provision for the use of other tools of development assessment

			2 months of life and should be used for all follow-up visits.	
3 24JUN2013	4.3	To meet inclusion criteria for study drug administration, families of potential study subjects will be asked if their male newborn has been tested for EDA mutations that confirm the XLHED diagnosis, either prenatally or postnatally. If genetic testing has been done, verbal consent from the family will be obtained to provide documentation of test results to the study site via a secure and confidential method including an option for electronic transmission. If not, the study site will provide a genotyping kit with an informed consent form directly to the family (no provision for fetal or amniotic fluid testing as part of this protocol). All genotyping costs will be covered by the study. It will be the responsibility of the family to have cord blood or a neonatal blood sample drawn and sent to the recommended genotyping laboratory.	To meet inclusion criteria for EDI200 administration, potential study subjects are required to have their XLHED diagnosis confirmed by genetic testing of the EDA gene and these test results relayed to the study site. EDA genetic testing itself is outside of the scope of this protocol. If requested, the families of prospective subjects in need of EDA genotyping will be referred to resources available to facilitate this testing. Consent from the family (written or verbal) will be obtained as part of the screening process to provide the study site with documentation of genetic testing results via a secure and confidential method including an option for electronic transmission.	Clarification of genetic testing done during screening
3 24JUN2013	4.5.1	New text added	It will be the Principal Investigator's responsibility to assess laboratory parameters against local reference ranges and to assess the clinical significance of any out of range values.	Clarification on assessment of lab values using both CTCAE criteria and local reference ranges
3 24JUN2013	4.6.2	The PI will report all SAEs to the Sponsor in a timely fashion, usually within 24 hours of awareness, by completing and faxing the SAE Report Form to CTI Safety as per directions	The PI will report all SAEs to the Sponsor in a timely fashion, within 24 hours of awareness, by completing and faxing the SAE Report Form to CTI Safety as per directions described in the	Word "usually" deleted as reporting requirements are within 24 hours

		described in the Study Reference Manual.	Study Reference Manual.	
3 24JUN2013	4.8	Unscheduled DSMB reviews will take place as outlined in Section 3.3.4-3.3.7 for single or accumulated adverse events.	Unscheduled DSMB reviews will take place as outlined in Section 3.3.4-3.3.7 for single or accumulated adverse events. Additional safety- related evaluations of one or more subjects may be requested by the DSMB based on findings through the 6 month, end-of-study visit.	Provision to allow for additional DSMB-requested procedures or visits
3 24JUN2013	5.5	New text added	The Sponsor or DSMB may request unscheduled visits either during the subject's participation in the Study or after his completion. The unscheduled visits may include additional safety-related evaluations (including blood sampling) based on findings through the 6-month, end-of-study visit.	Provision to allow for unscheduled visits

EXECUTIVE SUMMARY

X-linked hypohidrotic ectodermal dysplasia (XLHED) is a disorder of ectoderm development in which sweat and secretory gland hypoplasia predisposes affected infants to serious and potentially life-threatening hyperthermia and pneumonia (Clarke et al., 1987). Those XLHED patients who survive infancy face a host of ectoderm-related clinical conditions including failure to thrive, oligodontia and misshapen teeth, mid-face hypoplasia, eczema, chronic dry eyes, asthma, respiratory infections, sinusitis and chronic nosebleeds. XLHED is caused by inherited defects in the ectodysplasin gene (EDA, www.ncbi.nlm.nih.gov/omim) resulting in a deficiency of the ectoderm signaling protein EDA-A1. As is the general case with X-linked disorders, hemizygous XLHED males are more consistently and severely affected, while heterozygous XLHED females have a more variable phenotype.

In normal development, EDA-A1 acts as an ectoderm signaling molecule that binds specifically to the EDA-A1 receptor (EDAR) triggering initiation and maturation of ectoderm appendages into sweat and secretory glands, tooth buds and hair follicles. In the case of XLHED, EDA-A1 deficiency results in the absence or functional hypoplasia of the ectoderm appendages. There are no therapies currently available for XLHED that prevent or correct the underlying ectodermal abnormalities.

EDI200 is a fully humanized EDA-A1 replacement molecule under development as a novel therapeutic for XLHED. EDI200 comprises the human IgG1 Fc domain linked to the human EDA-A1 receptor-binding domain. In the course of normal ectodermal signaling, EDA-A1 monomers associate as trimers and higher order multimers that are required for activation of the EDA-A1 receptor (EDAR). The N-terminal Fc receptor portion of the EDI200 molecule serves to stabilize the intermolecular EDA-A1 associations required for EDAR binding, and to provide a potential mechanism for transplacental delivery (Miller, 2003).

On-target EDI200 activation of the EDA-A1/EDAR signaling pathway *in vivo* is evidenced by the remarkable phenotypic response in preclinical models. In XLHED-affected animals, EDI200 correction of EDA-A1 deficiency prenatally (mice) or postnatally (newborn mice and dogs) resulted in a significant and sustained improvement in the health of the treated animals (Gaide and Schneider, 2003; Casal et al., 2007; Mauldin et al., 2009). Postnatal studies in both mice and dogs demonstrated a consistent and restricted window of efficacy (Gaide and Schneider, 2003; Edimer Study NCD-11-200-005). These results support the clinical development of EDI200 as a therapeutic to be administered to XLHED-affected patients in the neonatal period or earlier.

This Phase 2 first-in-neonate study will enroll treatment-naïve, XLHED-affected newborns for EDI200 administration initiated within the first two weeks of life. All subjects will meet entry criteria including documentation of an EDA mutation associated

with XLHED. Following Baseline evaluations, EDI200 dosing will be initiated between day-of-life (DOL) 2 and 14, with each study subject receiving 2 doses/week for a total of 5 doses. This dosing regimen mirrors that used to enhance efficacy in the dog XLHED model, considered to be most relevant to the clinical study design. Comprehensive safety, pharmacokinetic (PK), immunogenicity and pharmacodynamic (PD)/efficacy evaluations of all neonate study subjects will initiate at study enrollment and continue throughout the dosing and follow-up period (to age 6 months).

The study will enroll 6-10 subjects in two cohorts, with a minimum of 3 male subjects per cohort. Given the challenge of identifying families where the potential study subject is yet to be born, it is expected that cohort size and time for recruitment will be variable. We anticipate enrolling subjects over a 12-18 month period. Cohort 1 study subjects will each be administered EDI200 IV at 3 mg/kg/dose x 5 doses, equivalent to 0.015 x the neonate no observed adverse effect level (NOAEL) of 200 mg/kg/dose (factor of 1:66) and well below the maximum safe starting dose in initial clinical trials as suggested by FDA guidance. This dose was associated with partial efficacy in the canine XLHED model considered most relevant to the clinical study, and was well tolerated by XLHED adults in the Phase 1 safety study (NCT01564225, www.clinicaltrials.gov)

All safety laboratory studies will be done at the individual study sites and available to the Data Safety Monitoring Board (DSMB) in real time. Following dosing of all subjects in neonate cohort 1, the DSMB will review the cohort 1 safety and PK data. If no new safety issues are identified then cohort 2 subjects will be enrolled and dosed at a ½ log increase to 10 mg/kg/dose IV, equivalent to 0.05 x the neonate NOAEL of 200 mg/kg/dose (factor of 1:20). This dose was associated with enhanced efficacy in the canine XLHED model. Prior to the dosing of XLHED neonates in cohort 2, the DSMB also will have reviewed the safety and PK data from XLHED adult cohort 2 subjects dosed at the same 10 mg/kg/dose and the same 5 dose regimen.

In the core study, primary outcome measures will be safety, PK and immunogenicity. Secondary outcome evaluations of pharmacodynamics (PD)/efficacy will incorporate growth and development parameters, frequency of infections and hospitalizations, facial development as monitored by computerized recognition of XLHED-associated features, and assessments of ectoderm-related physiologic functions using technologies that minimize risk to this population. From 6 months onward (end of data collection in the Phase 2 core study), the EDI200-exposed infants will be enrolled in a long-term extension study with yearly safety and age-appropriate PD/efficacy evaluations.

Although females often display a less severe phenotype this protocol allows for the inclusion of females in the study. Enrollment of XLHED-affected female newborns is based on the following: (1) newly published data reporting an increased risk for XLHED-affected females in abnormalities of growth, respiratory infections, dentition, eczema and dry eyes (Fete et al., 2014); (2) preclinical data on abnormal mammary gland

development in XLHED (Lindfors et al., 2013); and (3) both the Phase 1 adult safety study and all IND-enabling toxicology studies were conducted in male and female animals with no gender-associated safety findings (ECP-005 Clinical Study Report, Edimer Studies 1800-009 and 1800-010). Siblings of study subjects, both affected and unaffected, will be offered enrollment in an accompanying natural history sub-study including a medical history questionnaire and a one-time, non-invasive evaluation of current clinical condition (without study drug administration, X-rays or blood draws).

Given the consistent phenotype demonstrated in males with this X-linked disorder, genetic testing of male siblings will not be required to meet enrollment criteria. However, with the phenotype variability in XLHED-affected females, all females enrolled (affected and unaffected) in the sibling study, genetic testing is required. Only female siblings with confirmation of their genetic test status may be enrolled. The results from these genetically related, untreated siblings will provide comparative data for interpreting the clinical outcomes in treated study subjects.

SYNOPSIS

Title of Study	A Phase 2 open-label, dose-escalation study to evaluate the safety, pharmacokinetics, immunogenicity and pharmacodynamics/efficacy of EDI200, an EDA-A1 replacement protein, administered to infants with X-Linked Hypohidrotic Ectodermal Dysplasia (XLHED)
Name of Company	Edimer Pharmaceuticals, Inc.
Name of Finished Product	EDI200
Name of Active Ingredient	EDI200
Protocol Number	ECP-002
IND Number	109262
EudraCT Number	2012-003561-17
Objectives	Primary Objectives • To assess the safety, pharmacokinetics and immunogenicity of EDI200 administered to XLHED-affected neonates Secondary Pharmacodynamic/Efficacy Objectives • To assess EDI200 pharmacodynamics/ efficacy in the treatment of XLHED-affected neonates • To compare clinical and medical history data obtained from untreated siblings to that of the XLHED-affected neonate receiving study drug
Methodology	Phase 2 open-label, two cohort, dose-escalation study
Number of Subjects	• 6-10 XLHED-affected neonates for study drug administration • Siblings (XLHED-affected and unaffected) as historical controls
Diagnosis and Main Criteria for Inclusion	Neonates documented by genetic diagnosis to carry an EDA mutation associated with XLHED, and their siblings
Test Product Dose, Route of Administration	3 or 10 mg/kg/dose (IV)
Duration of Treatment	5 doses over 15 days
Pharmacodynamic/Efficacy Evaluations	• Growth and development

	• Infections and hospitalizations • Dentition • Facial development • Sweat gland number and function (males only) • Dry eye assessment • Thermoregulation • Skin biopsy for expression profile (males only)
Safety Evaluations	Safety laboratory blood tests, Vital Signs, Adverse Events
Pharmacokinetics Evaluations	Serial blood draws
Statistical Methods	The safety population will consist of all subjects who receive at least one dose of study medication. The PK population will consist of all subjects who receive at least one dose of study medication and have sufficient data points to obtain a plasma concentration by time profile. The PD/efficacy population will consist of all subjects who receive at least one dose of study medication and complete the follow-up assessments through at least month 2.

TIME AND EVENTS SCHEDULE – MULTI-DOSE EDI200 ADMINISTRATION

	Screening		Baseline	Treatment Phase										Follow-up Visits	Study Completion
	Prenatal[1] (Optional)	Postnatal[2] DOL 2 to DOL 12	DOL 2 to DOL 14[3]	TD 0	TD 1	TD 2	TD 4	TD 7	TD 11	TD 14	TD 15	TD 16	TD 21	Mon 2 & 4 of Life[4] (± 1 wk)	Mon 6 of Life[4] (± 2 wks)
Informed Consent	X	X	X												
Inclusion/Exclusion	X	X	X												
Genetic testing			X[5]												
Medical History	X	X[6]	X												
Safety Evaluations															
Physical Examination[7]			X	X	X		X	X	X	X	X		X	X	X
Safety Laboratory			X		X							X	X	X[8]	X
Immunogenicity			X									X		X[8]	X
Pharmacokinetic[9]			X	X	X	X				X		X	X	X[8]	X
PD/Efficacy															
Growth/Development			X											X	X
Dentition[10]			X												
Facial Development[11]			X												X
Sweat Assessments[12]			X											X[8, 13]	X
Dry eye Assessment			X											X[8, 13]	X
Thermoregulation[14]			X										X		
Skin biopsy sample[15]			X		X						X				
Study Drug				X			X	X	X	X					
Adverse Events/Con Meds[16]	X														

TIME AND EVENTS SCHEDULE – SIBLINGS OF STUDY SUBJECTS

	Study Enrollment	Evaluation
	From date of 1st dose study drug administered to affected sibling	Prior to Study Completion for affected sibling
Informed Consent	X	
Inclusion/Exclusion Criteria	X	
Medical History	X	
Safety Evaluations		
Physical Examination		X
Weight, Height, Vital Signs		X
XLHED-associated Outcomes		
Growth/Development		X
Infections/Hospitalizations		X
Dentition		X[17]
Facial Development		X[18]
Sweat Assessments		X
Pulmonary function[19]		X
eNO level[20]		X
Dry eye Assessment[21]		X
Adverse Events & Con Meds	X	

1. Optional prenatal screening enrollment is from end of first trimester through delivery date
2. Newborn's screening window for study inclusion is through DOL #12
3. Baseline evaluations must be completed by DOL #14
4. Follow-up visits at 2, 4 and 6 months of chronologic age
5. In the Screening process, confirmation of subject EDA genotype is required from the family. Under Baseline Events, EDAR genotyping for the phenotype-modifying polymorphism EDAR V370A will be a standard assessment (Cluzeau et al., 2012) but is not required prior to study drug administration
6. Medical history encompasses antenatal and perinatal findings including antenatal ultrasound imaging of tooth buds if performed (Ulm et al., 1998)
7. A full physical examination will be conducted at baseline, day 21, months 2, 4, and 6. With the full physical examination will be the following quantitative assessments: weight, height, head circumference and vital signs (temperature, blood pressure, heart rate and respiratory rate). A brief physical examination will be conducted at treatment days 0, 1, 4, 7, 11, 14 and 15. The brief physical examination will include overall appearance (normal or abnormal and if abnormal why), skin appearance, cardiovascular, pulmonary and abdominal evaluation. With the brief physical examination will be weight and a set of vital signs (temperature, blood pressure, heart rate and respiratory rate). On dosing days vital signs will also be collected pre- and post dosing as described in section 3.3.8.
8. Studies to be performed at 2 months but not at the 4-month visit.
9. PK samples drawn pre-EDI200 dosing and post-end of infusion at approximately the following time points:

	Pre-Dose	Post-Dose							
		15 (±5) min	3 (±.5) hrs	8 (±1) hrs	18 (±2) hrs	24(±2) hrs	48 (±4) hrs	168(±8) hrs	Age 2 months (±1 wk) & 6 months (±2 wks)
D0 (dose 1)	X	X	X	X		X	X		
D14 (dose 5)	X	X	X		X		X	X	X

10. Baseline lateral jaw film only. Dental evaluation to be performed in the long-term extension study will minimize the use of dental radiographs, and allow for substitution of dental imaging obtained as part of the routine care of XLHED patients.

11. Digital analysis of non-invasive 2D facial photographs is a technology under development jointly by the Sponsor and a private company and is being explored as a tool for monitoring change in craniofacial appearance. The algorithm assesses the subject's facial structures in the neonatal period and continues through photographs taken in the extension study.
12. Sweat assessments are done in male subjects only.
13. Sweat duct density and dry eye assessment done at 6 months only.
14. Thermoregulation assessment in the neonatal period is a well-documented procedure monitoring short-term temperature and vital sign response in a closed system (incubator). At an older age in the extension study, exercise-related thermoregulation will be assessed.
15. Skin biopsies are done in male subjects only.
16. Infections/hospitalizations as PD/efficacy endpoint will be captured through adverse events
17. No dental radiographs will be taken as part of this sibling sub-study. Subjects will be asked to provide copies of recent dental X-rays from an outside source.
18. Frontal and lateral facial photographs to be taken and baby picture (age up to 1 month) to be collected if available
19. Minimum age 5 years for pulmonary testing
20. Minimum age 4 years for eNO assessment
21. A more comprehensive dry eye assessment will be performed in children as opposed to the neonates

LIST OF ABBREVIATIONS

Abbreviation	Definition
2D	Two Dimensional
ADL	Activities of Daily Living
AE	Adverse Event
AUC	Area Under the Curve
BSID	Bayley Scales of Infant Development
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTGF	Connective Tissue Growth Factor
DDST	Denver Development Screening Test
DOL	Day of Life
DSMB	Data Safety Monitoring Board
EDA	Ectodysplasin A
EDA-A1	Ectodysplasin protein A1
EDAR	Ectodysplasin-A1 Receptor
EDC	Electronic Data Capture
eCRF	Electronic Case Report Forms
eNO	Exhaled Nitric Oxide
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
Lgr5	Leucine-Rich G-Protein Coupled Receptor
MedDRA	Medical Dictionary for Regulatory Activities
NCD	Nonclinical Document
NCI	National Cancer Institute
NOAEL	No Adverse Effect Level
OSDI	Ocular Surface Disease Index
PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetic
RNA	Ribonucleic Acid
SAE	Serious adverse event
Shh	Sonic Hedgehog

SUSAR	Suspected Unexpected Adverse Reaction
TD	Treatment Day
XLHED	X-Linked Hypohidrotic Ectodermal Dysplasia

PI AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

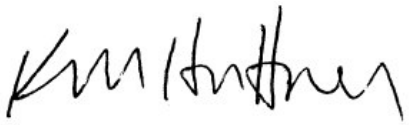
I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the conduct of the study.

PI's Signature* Date

Name of PI (Typed or Printed)

Institution Address*

Phone Number*



16JUL2014

Sponsor's Medical Monitor Signature Date

Kenneth Huttner, MD, PhD

Name of Medical Monitor (Typed or Printed)

* If the address or phone number of the PI changes during the course of the study, written notification will be provided by the PI to the Sponsor and will not require protocol amendment(s).

1 BACKGROUND

XLHED, the most common of the ectodermal dysplasias, is caused by inherited defects in the ectodysplasin (EDA) gene that disrupt synthesis and/or function of the primary translational product EDA-A1 (www.ncbi.nlm.nih.gov/omim). In normal development, EDA-A1 acts as an ectoderm signaling molecule that binds specifically to the EDA-A1 receptor (EDAR) triggering initiation and maturation of ectoderm appendages into sweat and secretory glands, tooth buds and hair follicles. The absence of normal EDA-A1 expression results in sweat and secretory gland hypoplasia predisposing XLHED-affected infants to serious and potentially life-threatening hyperthermia and pneumonia (Clarke et al., 1987). XLHED-affected children surviving infancy face a host of life-long ectoderm-related clinical conditions including failure to thrive, oligodontia and misshapen teeth, mid-face hypoplasia, eczema, chronic dry eyes, asthma, respiratory infections, sinusitis and chronic nosebleeds. As is the general case with X-linked disorders, XLHED-affected males are more consistently and severely affected, while XLHED-affected females have a more variable phenotype.

There are no therapies currently available for XLHED that prevent or correct the underlying abnormalities of ectoderm-derived structures. In two genetically confirmed animal models of XLHED, systemic administration of recombinant EDA-A1 (EDI200) in the prenatal (mice) or postnatal (newborn mice and dogs) settings corrected many of the defects in ectoderm development resulting in a significant and sustained improvement in the health of the treated animals (Gaide and Schneider, 2003; Casal et al., 2007). To date, data in both species has demonstrated a restricted efficacy window that closes after the first several weeks of postnatal life (Gaide and Schneider, 2003; Edimer Study NCD-200-11-005). This is consistent with the well-studied timeframe for ectoderm appendage development, and supports the clinical development of EDI200 as a therapeutic to be administered to XLHED-affected patients in the newborn period or earlier.

1.1 Rationale for Study

Study Drug - EDI200 is a fully humanized EDA-A1 replacement molecule designed for parenteral administration, comprising the human IgG1 Fc sequence linked to the human EDA-A1 receptor-binding domain. The N-terminal Fc receptor portion of the EDI200 molecule serves to facilitate and stabilize the intermolecular associations required for EDAR binding, as well as providing a potential mechanism for fetal delivery (Miller, 2003). Through its unique design, EDI200 retains the EDA-A1 receptor specificity as evidenced by the targeted phenotype response in preclinical XLHED models (Gaide and Schneider, 2003; Casal et al., 2007; Mauldin et al., 2009).

Safety and PK data in Adults - Following discussions with the FDA regarding the clinical development plan for EDI200 in a pediatric indication; a Phase 1 study in XLHED-affected adults was initiated (NCT01564225, www.clinicaltrials.gov) to develop human safety and PK data in anticipation of dosing XLHED-affected neonates. Selecting XLHED-affected adults for

the Phase 1 study provided a genetic and biologic relevance to XLHED-affected neonates. Enrolling adult XLHED-affected males and females: (1) supported dosing of male and female XLHED neonates in the current trial; and (2) initiated the collection of data necessary to support a future trial of maternal EDI200 administration. Identical dosage (mg/kg) and dosing regimens are planned for the adult and neonate XLHED studies.

Neonate Dosing Strategy: Age at Dosing Initiation; Dosing Regimen; Starting Dose

Age at Dosing Initiation – In both the mouse and dog XLHED models; early postnatal administration was associated with correction of clinically relevant abnormalities. Based primarily on the multi-dose dog data, study drug administration in this protocol is targeted to begin between day-of-life (DOL) #2 and DOL #14 (Edimer Study NCD-200-11-005).

Dose Regimen - The EDI200 dosing regimen proposed for the Phase 2 XLHED neonate study is a single course consisting of 5 doses administered at 2 doses/week. This regimen is based on results from the dog XLHED model which is most comparable to the human condition in developmental maturity at birth and in health-related endpoints (Casal et al., 2007; Edimer Study NCD-200-11-004). The 2-dose/week-regimen was incorporated into the GLP toxicology studies as well (Edimer Studies 1800-009 and 1800-010).

Starting Dose – No study-drug related adverse effects were observed at the highest EDI200 dose tested in both mouse and dog neonatal GLP toxicology studies, confirming a NOAEL of ≥200 mg/kg/dose (1800-009; 1800-010). Consistent with FDA guidelines for Maximum Starting Dose in Initial Clinical Trials, and incorporating a conservative approach to dosing in this vulnerable population, the first cohort of XLHED neonates will receive EDI200 at 3 mg/kg/dose IV, 0.015 x neonatal NOAEL (factor of 1/66). In the dog XLHED efficacy studies, dosing at 3 mg/kg/dose was associated with partial efficacy, which was enhanced significantly in animals receiving 10 mg/kg/dose (Edimer Study NCD-200-11-004). Safety and PK data from the Phase 1 adult study cohort treated with EDI200 at 3 mg/kg/dose x 5 doses over 15 days was reviewed by the DSMB with no reported study drug-related adverse events.

In the Phase 2 neonate study, the DSMB will review safety and PK data from neonate cohort 1, and in the absence of safety concerns, neonates will then be enrolled in cohort 2 and dosed at a pharmacologic half-log increase to EDI200 10 mg/kg/dose IV, equivalent to 0.05 x the neonatal NOAEL (factor of 1/20). Safety and PK data from the Phase 1 adult cohort 2, having received EDI200 at the same dose and the same dosing regimen, also will be reviewed by the DSMB prior to initiating dosing in neonate cohort 2. The dose for XLHED neonate cohort 2 is anticipated to maximize postnatal EDI200 efficacy based on the dog XLHED results (Edimer Study NCD-200-11-004).

Cohort enrollment - The Phase 2 neonate XLHED study is designed to enroll two cohorts of at least 3 male subjects each (cohort size determined by rate of enrollment and sponsor discretion), consistent with the practical aspects of study enrollment in ultra-rare orphan

disorders and the unique challenge of enrolling newborns. Enrollment and dosing of all subjects in neonate cohort 1 (3 mg/kg/dose) will be completed and reviewed prior to initiating dosing of subjects in neonate cohort 2 (10 mg/kg/dose).

Although females typically have a less severe phenotype this protocol allows for the enrollment of XLHED-affected female newborns based on the following: (1) newly published data reporting an increased risk for XLHED-affected females in abnormalities of growth, respiratory infections, dentition, eczema and dry eyes (Fete et al., 2014); (2) preclinical data on abnormal mammary gland development in XLHED (Lindfors et al., 2013); and (3) both the Phase 1 adult safety study and all IND-enabling toxicology studies were conducted in males and females with no gender-associated safety findings (ECP-005 Clinical Study Report, Edimer Studies 1800-009 and 1800-010).

Primary objectives - Safety labs, physical examination, vital signs, adverse events and concomitant medications, immunogenicity, and PK will be documented as outlined in the Time and Events schedule. The schedule for PK sampling, based on the preclinical and Phase 1 adult XLHED dosing results, incorporates a sparse sampling approach to limit the frequency and volumes of neonatal blood draws. The proposed PK sampling maximizes data collection for determining both the AUC and Cmax.

Pharmacodynamic/efficacy objectives - PD/efficacy endpoint assessments relevant to the biology and pathophysiology of XLHED are incorporated into the study design as outlined in the Time and Events Table. Consistent with the randomization of X-inactivation in XLHED-affected females, skin site-specific endpoints including confocal imaging, pilocarpine-induced sweat volume and biopsy for expression profile will be limited to male subjects.

- *Clinical endpoints* - growth and development (including feeding history), infections and hospitalizations (captured under adverse events).
- *Imaging assessments* - diagnostic dental radiographs (the post-treatment dental X-rays will be incorporated into the long-term extension study and hence are not described further in this protocol), antenatal ultrasound results for tooth bud development (if available as part of Obstetric care, documented in the Medical History), pre- and post-treatment facial photographs to assess changes in craniofacial features associated with XLHED and its correction.
- *Clinical biomarkers* - sweat duct number and induced sweat volume, thermoregulation and dry eye evaluation.
- *Molecular biomarkers* - skin biopsy for expression profile.

All affected and unaffected siblings of study subjects will be offered enrollment in a natural history sub-study evaluating the medical history and clinical condition of genetically related, untreated comparators for the study subjects. Given the consistent phenotype demonstrated in males with this X-linked disorder, genetic testing of male siblings will not be required to meet enrollment criteria. However, with the phenotype variability in XLHED-affected females,

only female siblings (both affected and unaffected) with confirmation of their genetic test status may be enrolled.

Study Duration - Total study duration for each subject receiving study drug will be approximately 6 months, including a treatment and safety/efficacy monitoring period. A long-term extension study for all subjects receiving study drug will continue safety and PD/efficacy evaluations. Study duration for siblings in the sibling sub study will be 1-2 days.

2 OBJECTIVES

2.1 Primary Objectives

To assess the safety, pharmacokinetics and immunogenicity of EDI200 administered to XLHED-affected neonates

2.2 Pharmacodynamic/Efficacy Objectives

- To assess the pharmacodynamics/efficacy of EDI200 administered to XLHED-affected neonates
- To compare clinical data and medical history obtained from untreated siblings to that of the XLHED-affected neonates receiving study drug

3 STUDY DESIGN

3.1 Multi-Dose EDI200 Administration

3.1.1 *Brief Description and Rationale for Study Design*

X-linked hypohidrotic ectodermal dysplasia (XLHED) is a disorder of ectoderm development associated with EDA gene mutations that lead to a deficiency of the ectoderm signaling protein EDA-A1. EDI200 is a fully humanized EDA-A1 replacement molecule under development as a novel therapeutic for XLHED. In two XLHED animal models, a single course of perinatal EDI200 administration resulted in a substantial correction of abnormalities in ectoderm development and a significant improvement in the health of the treated animals (Gaide and Schneider, 2003; Casal et al., 2007). These preclinical findings support the clinical development of EDI200 as a therapeutic to be administered to XLHED-affected patients in the neonatal period or earlier.

The open-label Phase 2 study of EDI200 administered to XLHED-affected neonates will enroll 6-10 subjects in two sequential cohorts. Each study subject will have documentation of an EDA gene mutation. Cohorts will be enrolled sequentially, i.e. the first subjects will all be enrolled in cohort 1, and only after cohort 1 safety evaluation by the DSMB will subjects be enrolled in cohort 2 for dosing at a higher level. Final cohort size will be determined by subject and site availability, with at least 3 subjects per cohort.

Although often females display a less severe phenotype this protocol allows for the enrollment of XLHED-affected female newborns based on the following: (1) newly published data reporting an increased risk for XLHED-affected females in abnormalities of growth, respiratory infections, dentition, eczema and dry eyes (Fete et al., 2014); (2) preclinical data on abnormal mammary gland development in XLHED (Lindfors et al., 2013); and (3) both the Phase 1 adult safety study and all IND-enabling toxicology studies were conducted in male and female animals with no gender-associated safety findings (ECP-005 Clinical Study Report, Edimer Studies 1800-009 and 1800-010).

The EDI200 dose for subjects in cohort 1 is 3 mg/kg/dose, consistent with the FDA Guidelines for Maximum Safe Starting Dose in Initial Clinical Trials based on the neonate NOAEL of $\geq$200 mg/kg/dose. This dose is anticipated to be associated with partial efficacy based on the dog XLHED studies. Safety laboratory results will be available to the DSMB in real time, and a formal DSMB safety and PK review will occur following completion of dosing in cohort 1. Additionally, the DSMB will have available to it safety and PK data from all XLHED-affected adult subjects from the Phase 1 adult safety study (NCT01564225, www.clinicaltrials.gov). In the absence of a safety signal or PK concern from DSMB review, XLHED neonates in cohort 2 will be dosed at 10 mg/kg/dose, a half-log pharmacologic increase to a dose anticipated to maximize clinical benefit based on the XLHED dog studies.

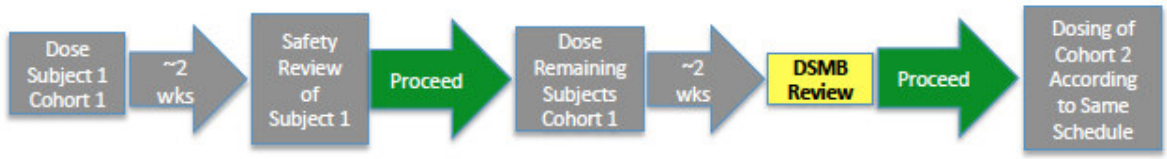
Primary outcome measures for all subjects will be safety, PK and immunogenicity. Study duration is 6 months with all subjects rolling over into a long-term extension study providing yearly evaluations. Pharmacodynamic/efficacy objectives in the Phase 2 neonate study will be limited by the timeline for ectodermal development that often exceeds 6 months, e.g. dentition. Therefore, several of these endpoints will be incorporated into the extension study protocol. There will be assessment of the following: (1) endpoints relevant to the common clinical findings in XLHED using age-appropriate technologies, e.g. growth and development, infections and hospitalizations, sweat duct counts and stimulated sweat production (males only), pre-treatment dentition, and thermoregulation; (2) change from baseline in craniofacial structures using a non-invasive facial recognition software program based on subject digital facial photographs (Appendix 1); and (3) change in molecular expression profile using skin biopsy samples obtained pre- and post-study drug exposure (males only).

3.1.2 *Starting and Target Dose/Dosing Regimen*

The proposed starting dose is consistent with the FDA Guidelines for Maximum Safe Starting Dose in Initial Clinical Trials, based on the neonate GLP toxicology studies in two species that demonstrated a NOAEL of $\geq$200 mg/kg (MPI Study 1800-009 and 1800-010). Cohort 1 subjects will be dosed with EDI200 at 3 mg/kg/dose IV, 0.015 x neonate NOAEL (factor of 1/66). The proposed dosing regimen of 2 doses/week x 5 doses, beginning within the first 2 weeks of life, is supported by the dosing regimen in the GLP toxicology studies. This dose and dosing regimen is in the range of anticipated partial efficacy in the dog XLHED model, considered the most relevant species for endpoint assessment.

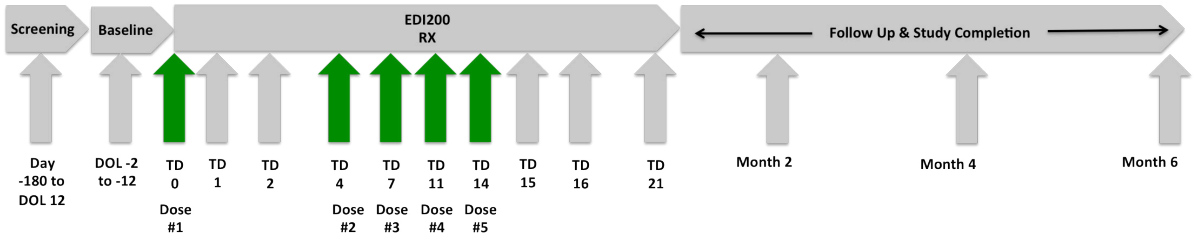
Prior to enrolling subjects in neonate cohort 1, the DSMB reviewed safety and PK data from cohort 1 in the Phase 1 XLHED study (NCT01564225) where adult XLHED subjects were administered EDI200 at the same dose (3 mg/kg/dose) and dosing regimen (5 doses total at 2 doses/week). No study drug-related adverse events were reported. In neonate cohort 1, the first subject enrolled will complete dosing followed by a ~2-week safety review. If no safety concerns are observed, the remaining cohort 1 subjects will begin dosing. Dosing for individual subjects will be on a mg/kg basis.

Once all subjects in neonate cohort 1 have received their IV dosing, the DSMB will review safety and PK data. In the absence of safety concerns following DSMB review of cohort 1 data, neonates in cohort 2 will be dosed at a pharmacologic half-log increase to 10 mg/kg/dose, 0.05 x neonate NOAEL (factor of 1/20), following the same 5-dose regimen (see figure below). The dose and dosing regimen for neonate cohort 2 is in the range anticipated to maximize postnatal efficacy based on results from the dog XLHED model. Dosing of subjects in cohort 2 is sequential as described in cohort 1. Subject enrollment and cohort initiation will be according to the following schedule:



The study will be conducted in age-appropriate clinical facilities by medical staff with appropriate levels of training and expertise and an understanding of the investigational medicinal product, its target and mechanism of action. There will be immediate access to facilities for the treatment of medical emergencies including an Intensive Care Unit.

The study timeline and visit dates for each subject are as follows:



3.1.3 *Screening*

A family with a fetus/newborn with a clinical suspicion of XLHED may inquire to receive study information by phone, email or directly at a study site (also available on www.clinicaltrials.gov). If the family then wishes to be considered for study participation, they have the following options:

1. Prenatal Screening Enrollment (optional): the family of a fetus at risk for XLHED may provide Informed Consent (ICF1) for data collection to begin in order to evaluate eligibility for newborn EDI200 treatment (see Sections 3.3.1 and 3.3.2). Entering the screening process early will allow for discussion and planning to minimize the potential family disruption that is likely to accompany early postnatal transfer to the study site if the subject is to be enrolled in the treatment protocol. The language of ICF1 will state clearly that once all Inclusion/Exclusion (I/E) criteria are met, an additional Informed Consent (ICF2), obtained postnatally, will be required in order to enroll the XLHED-affected neonate into the treatment portion of the study. The enrollment window for treatment encompasses the period from DOL #2 through DOL #12 (allowing a minimum of two days for transfer to the study site and baseline assessments prior to DOL #14, the last day study drug dosing can be initiated).

2. Postnatal Screening Enrollment: in the absence of Prenatal Screening Enrollment, the family of a newborn at risk for XLHED may provide Informed Consent (ICF1) for data collection to begin in order to evaluate eligibility for the newborn EDI200 treatment (see Sections 3.3.1 and

3.3.2). The language of ICF1 will state clearly that once all Inclusion/Exclusion (I/E) criteria are met, an additional Informed Consent (ICF2) will be required in order to enroll the XLHED-affected neonate into the treatment portion of the study. The enrollment window for treatment encompasses the period from DOL #2 through DOL #12 (allowing a minimum of two days for transfer to the study site and baseline assessments prior to DOL #14, the last day study drug dosing can be initiated).

A key inclusion criterion for the treatment protocol is verification of the XLHED diagnosis through EDA mutation testing. As part of the screening process, genetic testing results may be provided by the family to the study site via a secure and confidential method including the option for electronic transmission. If genotyping confirmation is not available at the time of Screening Informed Consent, the families of prospective subjects will be referred to resources available to facilitate rapid genotype testing at an accredited laboratory.

Families may be considering delivery at a clinical study site to facilitate treatment of their XLHED-affected son as soon as possible after birth. Any such decision is outside of this protocol and would be a private matter between the family, their health care providers, their insurance company, and the delivery service at the study site. Delivery at the study site would not commit the family to have their newborn participate in the treatment protocol, nor would it commit the PI and study site to enroll the XLHED-affected neonate unless and until he met all the required I/E criteria and a treatment Informed Consent (ICF2) was signed by both parents (if reasonably available).

If the XLHED-affected neonate meeting inclusion/exclusion criteria is not born at the study site, the study team will assist in and cover all reasonable expenses associated with his/her transfer to the site. If medical transport is required, this will occur under specific Informed Consent (ICF-T) requiring signatures of both parents (if reasonably available). The window for transfer to the study site must allow for the neonate to complete Baseline evaluations in a timely manner prior to DOL #14.

3.1.4 *Baseline*

Baseline evaluation will begin with confirmation of treatment inclusion/exclusion criteria and documentation of relevant family, pregnancy and neonatal medical history. Baseline assessments of the XLHED-affected infant as described below are to be completed prior to first dose study drug. To date, there is little data published describing evaluation techniques for XLHED patient in the newborn period. The Sponsor has experience with using the novel, minimally invasive technologies that are incorporated into this study protocol (www.edimerpharma.com/Publications and News/Publications and Abstracts)

In this Phase 2 protocol, baseline assessments of the neonate study subjects will serve three purposes. First, they will verify the general health of the XLHED-affected infant including documentation of developmental status and full physical examination. Second, blood samples

will be collected for pre-treatment safety laboratory values, documentation of the absence of EDI200 and anti-EDI200 antibodies, and genotyping of the EDAR V370A polymorphism that has the potential to modify the XLHED-phenotype. Third, they will document pre-treatment ectoderm status related to EDA-A1 deficiency, including sweat duct number (males only), induced sweat volume (males only), presence/absence of dentition on lateral jaw radiograph, dry eyes, digital 2D facial photograph for XLHED facial appearance, thermoregulation imbalance and skin biopsy for expression profile (males only).

3.1.5 *Treatment Period*

The subject will be admitted to the study site during the entire dosing period. The schedule of events for this portion of the study is presented in the Time and Events Table. In each cohort, the first subject enrolled will complete the 15-day dosing period and undergo monitoring for an additional week at the study site. The site and Sponsor Medical Monitors will then review all AE and safety laboratory data. In the absence of any clinically significant AE's the remaining cohort subjects may begin dosing. It is anticipated that the timeframe from last dose of the first cohort subject through AE review will be approximately 2 weeks.

Each subject will be administered 5 doses of EDI200, administered IV on Treatment Days (TD) 0, 4, 7, 11 and 14, with vital sign monitoring during and for 24 hours following each dose of study drug. The Treatment Day for doses two through five may be $\pm$1 day, but doses must be at least 48 hours apart. Subjects in cohort 1 will be dosed at 3 mg/kg/dose calculated on Baseline weight.

On TD 0, subjects will have the following evaluations performed prior to dosing: brief physical exam, AE and concomitant medication assessment. Subjects will be administered dose 1 of study drug with vital sign monitoring during and for 24 hrs post-dose. Full details of the vital sign monitoring plan are described in Section 3.3.8. Sparse PK sampling time points post-dosing are described in Section 4.5.2.

On TD 1, subjects will have the following evaluations performed: brief physical exam, AE and concomitant medication assessment, safety laboratories, PK sampling and skin biopsy (males only) for expression profile (both approximately 24-hour post dose 1).

On TD 2, subjects will have the following evaluations performed: AE and concomitant medication assessment and PK sampling (approximately 48-hour post dose 1).

On TD 4, subjects will have the following evaluations performed prior to dosing: brief physical exam, AE and concomitant medication assessment. Subjects will be administered dose 2 of study drug with vital sign monitoring during and for 24 hrs post-dose.

On TD 7, subjects will have the following evaluations performed prior to dosing: brief physical exam and AE and concomitant medication assessment. Subjects will be administered dose 3 of study drug with vital sign monitoring during and for 24 hrs post-dose.

On TD 11, subjects will have the following evaluations performed prior to dosing: brief physical exam and AE and concomitant medication assessment. Subjects will be administered dose 4 of study drug with vital sign monitoring during and for 24 hrs post-dose.

On TD 14, subjects will have the following evaluations performed prior to dosing: brief physical exam and AE and concomitant medication assessment, and PK sampling. Subjects will be administered dose 5 of study drug with vital sign monitoring during and for 24 hrs post-dose. Sparse PK sampling time points post-dosing are described in Section 4.5.2.

On TD 15, subjects will have the following evaluations performed: brief physical exam, AE and concomitant medication assessment, and a skin biopsy (males only) obtained approximately 24 hours after administration of the last dose of study drug.

On TD 16, subjects will have the following evaluations performed: AE and concomitant medication assessment, safety laboratories, immunogenicity sampling, and PK sampling (approximately 48-hour post dose 5).

On TD 21, subjects will have the following evaluations performed: full physical examination, AE and concomitant medication assessment, post-treatment thermoregulation assessment, safety laboratories and PK sampling (approximately 168-hour post dose 5).

The remainder of the study procedures through Month 6 are described in the post-treatment section, Section 3.1.6.

Dose escalation in XLHED neonate cohort 2 will not occur until a review of safety and PK data from XLHED neonate cohort 1 has been completed by the DSMB, approximately three weeks after the last subject is dosed in cohort 1. Assuming no safety or PK concerns following DSMB review, subjects in XLHED neonate cohort 2 will be dosed with EDI200 at 10 mg/kg/dose IV, a pharmacologic half-log increase. As part of the safety-monitoring program, prior to dosing subjects in neonate cohort 2 the DSMB will have reviewed safety and PK data from adult cohort 2 in the Phase 1 adult XLHED study where subjects received EDI200 at the same dose (10 mg/kg/dose) and dosing regimen (5 doses total at 2 doses/week).

3.1.6 *Post-Treatment Follow Up*

The post-treatment visits at Months of Life 2, 4 and 6 are designed to capture safety, immunogenicity and PD/efficacy data at appropriate time points following study drug exposure. In addition, PK data will be collected at Months of Life 2 and 6 visits. The post-treatment frequency of visits to the study site represents a balance between the acquisition of

informative data and minimizing the travel stresses for the infant subject and his family. These evaluations will not supplant the subject's normal well-child care visits and immunizations by his primary care provider.

At Month 2 of life, subjects will have the following evaluations: full physical exam, AE and concomitant medication assessment, safety laboratories, PK and immunogenicity sampling, and PD/efficacy evaluations including growth and development and induced sweating (males only). Expected stay at the study site location (i.e. within the vicinity of the study site) is 1-2 days.

At Month 4 of life, subjects will have the following evaluations: full physical exam, AE and concomitant medication assessment, and PD/efficacy evaluations including growth and development. Expected stay at the study site location (i.e. within the vicinity of the study site) is 1-2 days.

At Month 6 of life, subjects will have the following evaluations: full physical exam, AE and concomitant medication assessment, safety laboratories, PK and immunogenicity sampling, and PD/efficacy evaluations including growth and development, induced sweating and sweat duct imaging (males only), dry eye assessment and digital facial photographs. Expected stay at the study site location (i.e. within the vicinity of the study site) is 1-2 days.

The conclusion of the core study is defined as the last visit of the last participant.

3.2 XLHED-Affected and Unaffected Siblings of Study Subjects

All siblings (including multiple siblings of a single neonate) of enrolled XLHED-affected neonates will be offered the opportunity to participate in a non-invasive evaluation providing historical control data for this open-label study. The technologies involved will be modeled on the core study evaluations, with the exception that no X-rays will be taken; no blood draws and no tissue sampling will be involved. The evaluations will take place at the study site and will include Informed Consent and Assent, if applicable, medical history, physical examination, vital signs including weight and height, digital facial photographs (frontal and lateral), growth and development assessments, induced sweating and sweat duct imaging (males only), pulmonary function testing and eNO levels when age-appropriate (see Time & Events Schedule), dry eye evaluation and dental examination. Siblings will be asked to provide copies of their most recent dental radiographs. Expected stay at the study site location (i.e. within the vicinity of the study site) is 1-2 days.

3.3 Study Subjects

This Phase 2 study will enroll 6-10 XLHED-affected neonates for study drug administration, and includes the optional enrollment of all siblings, both affected and unaffected, for non-invasive evaluations.

3.3.1 *Inclusion Criteria*

Subjects for study drug administration must meet all of the following criteria to be enrolled:

1. Genetic confirmation of an XLHED diagnosis.
2. Subject must be at least 48 hours age and no older than 14 days.
3. Subject will have reached term (defined as 37 weeks gestation or older) prior to receiving first dose study drug.
4. Written informed consent of both parents (if reasonably available) must be obtained for treatment of their XLHED-affected infant.
5. Neither mother nor the XLHED-affected infant known to have received an investigational study drug in the 9 months prior to study subject enrollment in this study.
6. No major medical issues that the PI considers a contraindication to participation.

Siblings of subjects receiving study drug must meet all of the following criteria to be enrolled in the natural history sub-study (no age limit involved):

1. Provide written informed consent/assent.
2. A full or half-sibling of a study subject where the study subject has received at least one dose of study drug in the Phase 2 XLHED Neonate Study and has not yet completed the study.
3. Male siblings may be considered affected or unaffected based on clinical history. Due to the phenotypic variability associated with X-inactivation, female siblings (both affected and unaffected) will be required to have genetic confirmation of XLHED status.
4. No major medical issues that the PI considers a contraindication to participation.

3.3.2 *Exclusion Criteria*

Subjects for study drug administration who meet any of the following criteria cannot be enrolled in this study:

1. Medically significant postnatal complications or congenital anomalies outside of those considered associated with the diagnosis of XLHED.

Siblings of subjects receiving study drug who meet any of the following criteria cannot be enrolled in the natural history sub-study:

1. Known hypersensitivity to pilocarpine or pilocarpine-like muscarinic agonists.
2. Known hypersensitivity to lidocaine or lidocaine-like agents.
3. Presence of pacemaker.

4. Subjects who are not able or are not willing to comply with the procedures of this protocol.
5. Subject has a condition, which in the opinion of the PI would not allow for safe conduct of the study.

3.3.3 *Withdrawal or Removal of Subjects from the Study*

Study subjects/guardians may elect to discontinue study subject participation and withdraw from the study at any time without prejudice. The PI or Sponsor may withdraw a subject from participation in this study for any of the following reasons:

- A protocol violation occurs,
- The subject is not compliant with study procedures,
- A serious or intolerable adverse event occurs,
- The Sponsor or PI terminates the study, or
- The subject/guardian requests to be discontinued from the study.

A discontinuation occurs when an enrolled subject ceases participation in the study prior to completion of the protocol, regardless of the circumstances. The PI will determine the primary reason for discontinuation, and it will be recorded in the case report form and in the subject's research record. A discontinuation must be reported immediately to the Sponsor if it is due to a serious adverse event. The PI will provide or arrange for appropriate follow-up for such subjects (if required), and document the course of the subject's condition. In all cases of subject discontinuation, an attempt should be made to obtain the End-of-Study evaluations at their last study visit.

3.3.4 *Subject, Cohort or Study Suspension/Termination*

The Sponsor and/or the DSMB have the right to close this study at any time for safety or administrative reasons, although this should occur only after consultation between involved parties. The IRB/IEC and all relevant local National Competent Authorities must be informed.

3.3.5 *Subject Stopping Criteria*

- All AE and safety laboratory results will be available to the Medical Monitor, PI and DSMB in real time.
- For any Grade 2 or 3 adverse event (AE) defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v4.0; Appendix 2) that is deemed possibly, probably or definitely related to study drug treatment, individual subject dosing will be held pending review and recommendations of the Medical Monitor.
- If a subject misses a single dose and then is restarted, that dose will not be made up but all subsequent doses will be administered on schedule.
- If a subject misses two consecutive doses then dosing will not be restarted, but all study follow-up visits will occur as originally scheduled.

3.3.6 *Cohort Stopping Criteria*

The study design has only one cohort being dosed with study drug at any given time. Dosing of all subjects within a cohort will be suspended for:

- Two or more individuals develop a Grade 2 or 3 AE in a similar system organ class deemed possibly, probably or definitely related to study drug treatment (CTCAE v4.0), or
- For any Grade 4 adverse event (classified as severe or life-threatening) or a serious adverse event (SAE), regardless of drug-relatedness.

In the case where cohort dosing has been suspended, DSMB review of the AEs with the Medical Monitor, study PI and Sponsor will be required prior to discussing with a subject's family the option of restarting study drug or to enrolling additional subjects in the cohort. Missed doses will not be made up. Any subject missing two consecutive doses will not be restarted on treatment, will not be considered to have completed the dosing regimen, but will have all study follow-up visits as originally scheduled. If the DSMB safety review concludes that cohort dosing may continue, an additional subject may be added to the cohort for each subject that does not complete the dosing regimen.

In the case where a DSMB safety review concludes that a cohort should not continue dosing, no additional doses will be administered to subjects in that cohort, no additional subjects will be enrolled in that cohort, and all follow-up visits for enrolled subjects will occur as originally scheduled. The Sponsor will notify both the relevant National Competent Authorities and the local IRB/IEC of the action taken. The scheduled dose escalation cohorts will be suspended, although a more conservative dose escalation strategy may be considered for a subsequent cohort, requiring DSMB, relevant National Competent Authorities and study site IRB/IEC approval.

3.3.7 *Study Stopping Criteria*

The Sponsor and/or the DSMB have the right to close this study at any time for safety or administrative reasons, with timely notification of the relevant National Competent Authorities.

Permanent halting of dosing in any cohort by the DSMB related to safety concerns will trigger an automatic review of study termination by the DSMB in communication with the Medical Monitor, study PI, and Sponsor. If it is determined that study dosing should be terminated, all follow-up visits will occur as originally scheduled for subjects having received one or more doses of study drug. Study Sponsor assumes responsibility for reporting premature study termination to all regulatory authorities and institutional review boards.

Should the study be closed prematurely, all study materials (except documentation that has to remain stored with the PI) must be returned to the Sponsor. The PI will retain all other documents until notification given by the Sponsor for destruction.

3.3.8 *Treatment*

EDI200 study drug will be provided as a sterile solution for intravenous infusion in 3 ml glass vials, approximately 2.1 ml/vial at a concentration of approximately 5 mg/ml. Vials will be labeled according to local regulations and Sponsor standards. All study drug supplies should be stored frozen at -60 °C to -90 °C.

Dosing of EDI200 will vary by cohort. Study drug administration will be as follows:

Cohort	Number of subjects	Dose	Number of Doses	Study Day of Administration
Cohort 1	3-7	3 mg/kg	5	0, 4, 7, 11, 14
Cohort 2	3-7	10 mg/kg	5	0, 4, 7, 11, 14

The weight used to calculate study drug dose will be the subject's Baseline weight for all doses. If during the treatment period a subject experiences a change in weight of >10% from Baseline, the PI(s) and the Medical Monitor will review the option of adjustments to the subject's dosing.

EDI200 will be **thawed to room temperature** on the day of dosing, pooled in syringe(s) and administered via a syringe pump infusion system. The study drug shall be administered by slow IV infusion over at least 30 min, not to exceed 5 ml/kg/hour or 8.5 mg/min EDI200, in order to minimize the risk of infusion-related AE (refer to Investigational Brochure, Section 6.2). For more information on the preparation of EDI200 see the Pharmacy/Investigator Manual.

Examples are shown in the table below.

Subject Weight	EDI200 Dose (mg/kg)	Total Dose EDI200	EDI200 Conc (mg/ml)	Vol	Vol/kg	Minimum Infusion Time	ml/kg/ hr	EDI200 mg/min
3 kg	3	9 mg	5	1.8 ml	0.6 ml/kg	0.5 hrs	1.2	0.3
3 kg	10	30 mg	5	6 ml	2.0 ml/kg	0.5 hrs	4	1.0
4 kg	3	12 mg	5	2.4 ml	0.6 ml/kg	0.5 hrs	1.2	0.4
4 kg	10	40 mg	5	8 ml	2.0 ml/kg	0.5 hrs	4	1.3
5 kg	3	15 mg	5	3 ml	0.6 ml/kg	0.5 hrs	1.2	0.5
5 kg	10	50 mg	5	10 ml	2.0 ml/kg	0.5 hrs	4	1.7

During study drug administration and for 24 hrs following infusion the subject will have continuous heart rate and respiratory rate monitoring. A full set of vital signs including temperature, blood pressure, heart rate and respiratory rate will be documented on the following schedule:

- Pre dosing - a single set of vital signs within 1 hour of initiating dose infusion
- Post dosing:
    - 15 min after end of infusion,
    - 1 hr and 4 hrs after end of infusion,
    - then q4 hrs up to 24 hrs after end of infusion

If the unit in which the subject is receiving study drug requires additional monitoring, then that data will be added to the subject's record.

The intravenous site will be assessed for patency and signs of local irritation prior to the start of the infusion, every 30 minutes during infusion, and at the end of study drug infusion.

Doses 2-5 are scheduled for study days 4, 7, 11 and 14 respectively in both cohorts. If the subject is unable to be dosed on the specified day, a window of $\pm$24 hours is acceptable. However, there must be a minimum of two days between any two doses. The calendar date and 24-hour clock time of the beginning and end of each infusion will be recorded on the CRF. The dates and timing of PK sampling around dose 5 will be adjusted for any change in dosing schedule.

It is the responsibility of the clinical investigator to ensure that all study drug received at the site will be inventoried and accounted for throughout the study. Study drug must be handled strictly in accordance with the protocol and the container label and will be stored in a limited access area under appropriate environmental conditions. The investigator agrees neither to dispense the study drug from, nor store it at any site other than the study site locations agreed upon with the sponsor. Study drug should be dispensed under the direction of the investigator.

Study drug will be supplied only to subjects participating in the study. Study drug may not be relabeled or reassigned for use to other subjects. The dispensation and use of study drug must be documented on the Drug Accountability Form. Used and unused study drug must be available for verification by the sponsor's site monitor during on-site monitoring visits. The destruction or return to the sponsor of used or unused study drug will be approved by the sponsor and documented on the Drug Return Form.

4 STUDY EVALUATIONS

4.1 Medical Questionnaires

Two questionnaires are provided - one designated for the mother and XLHED-affected neonate (Appendix 3) and one designated for siblings of an enrolled neonate (Appendix 4). The former includes family history related to XLHED, pregnancy, labor and delivery, and neonatal data. The latter includes general medical history with an emphasis on issues common to XLHED-affected patients. This questionnaire will be used for both affected and unaffected siblings.

4.2 Pharmacodynamic/Efficacy Evaluations

Assessment of PD/efficacy endpoints will be performed on all subjects. The Sponsor will provide any equipment and training required for assessments.

4.2.1 *Growth and Development*

Cross-sectional data in patient populations with hypohidrotic ectodermal dysplasia consistently reports poor growth in infancy, most commonly poor weight gain and feeding issues, and an elevated risk of abnormal development (Clarke et al., 1987; Motil et al., 2005; Blüschke et al., 2010). The growth assessments will consist of feeding history as well as measurements of weight, length, and head circumference taken at study visits as part of the physical examination and plotted on standardized growth curves for newborns. The initial physical examination will include assessment of standard developmental milestones, and will be augmented at Months 2, 4 and 6 by a validated, standard of care infant assessment tool. Examples of such tools include but are not limited to the Bayley Scales of Infant Development II (BSID-II) and III (BSDI-III) and the Denver Development Screening Test II (DDST II) (Black and Matula, 2000). Whichever tool is selected should be designed for down to age 2 months of life and should be used for all follow-up visits.

4.2.2 *Thermoregulation*

XLHED-affected neonates and infants have a well-documented abnormality of thermoregulation (heat intolerance) and as a consequence are at elevated risk for life-threatening hyperthermia under unmonitored conditions (Clarke et al., 1987; Blüschke et al., 2010). At present there are no validated genetic, clinical or physiologic markers that identify the level of risk for a given XLHED-affected patient. In this protocol, assessment of thermoregulatory risk for an XLHED-affected neonate will provide valuable information for the family in preparing for a safe transition to home. Additionally, demonstration in the long-term extension study of an improved and sustained thermoregulatory improvement may be a key efficacy element in the response to study drug. Thus it is a relevant and appropriate evaluation in this protocol to assess thermoregulation of study subjects under closely monitored conditions with direct physician observation.

Thermoregulation reflects both sweat and insensible losses from the respiratory tract, both organ systems with compromised function in XLHED (Chawla et al., 2008; Clarke et al., 1987; Zankl et al., 2001; Casal et al., 2007; Seeliger et al., 2005). For term newborns placed inside a heated isolette, there is a wealth of validated clinical data on how to perform thermoregulation studies safely and what are the normal response parameters (e.g. Hey, 1975; Sjors et al., 1997; Stothers and Wagner, 1984; Sulyok et al., 1976). Healthy term babies reach the point of having to sweat to maintain body temperature at an isolette temperature of approximately 34°C. For thermoregulation assessment the study subjects will be placed unbundled in an isolette at a starting temperature of no more than 33°C in the ICU with continuous vital sign monitoring including respiratory rate, heart rate and body temperature. Isolette temperature will be held at the starting temperature for 0.5 hours for initial adaptation and baseline vital signs, following which it will be raised stepwise by 1-1.5°C every 30 minutes until reaching 36.5°C to assess infant response (Rutter and Hull, 1979). Total observation time is anticipated to be no more than 3 hours.

Strict stopping criteria will be in effect including: (1) a body surface temperature of ≥37.9°C (Rutter and Hull, 1979); (2) a noticeable change in behavior, e.g. uncontrolled crying; or (3) a sustained heart rate or respiratory rate outside of the normal range (HR 120-160 per minute; respiratory rate 40-60 per minute; Cloherty et al. 2004). With any of these changes or at the discretion of the study physician monitoring the assessment, the subject will be removed from the isolette to an unheated observation table until all vital signs and physical examination return to Baseline. Additional interventions are not anticipated, but will be at the discretion of the monitoring physician and the ICU staff.

In this exploratory endpoint, each subject's pre-dosing response to this short and controlled environmental challenge will be compared with the published literature and with the result of thermoregulation assessment after EDI200 dosing. Additional assessments of thermoregulation and heat tolerance are not standardized for ages 2-6 months but will be included as efficacy endpoints in the long-term extension study.

4.2.3 *Eccrine Structures (males only)*

4.2.3.1 Sweat Duct Density

Sweat duct density (number/cm^2) from at least two different sites on the soles of the feet (newborns and infants) or palms (siblings age ≥1 year) will be determined through analysis of images collected by direct visualization with an approved device, the Lucid VivaScope 1500 (www.lucid-tech.com). This technology has been tested in controls and XLHED-affected males from the newborn period to adulthood without complication (Dietz et al., 2013; Huttner et al., 2012; ECP-005 Clinical Study Report). An adhesive ring will be placed on the subject's palm/sole to which the VivaScope will be attached via a magnetic lock. A series of photographs will be

taken of an area approximately 6mm X 6mm. An individual trained in the use of this device will be involved in the acquisition of all images.

Up to two independent image readers trained in the reading of VivaScope images will interpret the images and provide sweat duct counts for inclusion with the study data. If there is a discrepancy in their counts of 10% or greater on an individual image, then both readers will reinterpret the same image and a final assessment made as an average of the repeat sweat duct counts. To account for growth during the study, all sweat duct counts will be adjusted for body surface area (Haycock et al, 1978).

4.2.3.2 Sweat Rate Testing

Sweat rate assessment following cholinergic stimulation is a technique used commonly in clinical trials as reported for the evaluation of distinct conditions including orthostatic hypotension, diabetes, growth hormone deficiency, Parkinson's disease, hypohidrosis, and Fabry's disease (Itoh et al., 2003; Low et al., 1983; Ramaswami et al., 2007). Maximal sweating on the volar lower arm surface of each subject will be induced by pilocarpine iontophoresis followed by sweat collection using the Macroduct Sweat Collection System developed primarily for sweat collection and analysis in the diagnosis of Cystic Fibrosis from the newborn period on (www.wescor.com). The Collection System consists of the Webster Sweat Inducer, Pilogel® Iontophoretic Discs and Macroduct Sweat Collectors. The Macroduct Sweat Collection System is approved for subjects of all ages including neonates (Mastella et al., 2000) and the manufacturer provides adequate directions for the device's use.

Pilogel® Iontophoretic Discs are unique gel reservoirs of pilocarpinium ions that are simple and safe to use in the iontophoretic stimulation of sweat. A Pilogel® disc is inserted into each of the recessed stainless steel electrodes, which are then attached to the subject. The Webster Sweat Inducer is activated by a start switch subsequently delivering a safe and optimal quantity of pilocarpine for gland stimulation (equivalent to five minutes iontophoresis at 1.5 mA) followed by an automatic, programmed stop.

Following completion of the pilocarpine iontophoresis the Webster Sweat Inducer electrodes and discs are removed from the subject, the application site is wiped once with alcohol, and a Macroduct Sweat Collector is placed over the site of one electrode. The Macroduct Sweat Collector is held in place for approximately 30 minutes using a Velcro Macroduct Strap. Sweat volume is determined from microliter markings on a collection coil diagram.

Individuals trained in the use of the Macroduct Sweat Collection System will be involved in both procedures and the acquisition of the data. The manufacturer of the iontophoresis device does report the rare occurrence (1 in 50,000) of small skin burns at the site of application, and physicians will be available on site to evaluate any adverse event occurrence.

4.2.4 *Pulmonary Function Testing and eNO levels*

Pulmonary function testing will be performed in the sibling sub-study on all subjects age 5 years and older at a laboratory experienced with pediatric subjects. Additionally, levels of exhaled nitric oxide (eNO) as an indicator of pulmonary inflammation will be quantified non-invasively with an age-group appropriate device in all siblings age 4 years and older.

4.2.5 *Dry Eye Assessment*

The eye examination will be performed by an ophthalmologist experienced in assessments of tear film and ocular surface in infants as well as children and adults. In newborns and infants, the examination will document the presence/absence of signs of infection and irritation, as well as a tear film break-up time. For children 5 years or older (sibling sub-study) the assessment will also include the Shirmer test for rate of tear production and the OCULAR SURFACE DISEASE INDEX© questionnaire (Appendix 5).

4.2.6 *Skin Biopsy (males only)*

Three mm diameter punch biopsies of skin will be obtained from the upper outer thigh area. Sites will follow their institutions standard practice with regard to biopsy procedure. The biopsy site may require absorbable suture(s). RNA isolated from the skin biopsies will be assayed in expression analyses to establish a biochemical response to EDI200 treatment in these EDA-deficient subjects. Genes to be evaluated include but are not are not limited to those involved in the EDA/EDAR pathway, e.g. EDAR, CTGF (connective tissue growth factor), Shh (sonic hedgehog) and Lgr5 (leucine-rich G-protein coupled receptor). For each study subject, comparisons will be made between the expression profiles obtained at Baseline, after the first and the last dose of EDI200.

4.2.7 *Dental Imaging/Examination*

The absence of tooth buds is a key confirmatory finding in phenotype assessment of an XLHED-affected neonate and can be determined from a lateral radiograph (Swischuk, 2003). Radiation exposure will be minimized in this study with a single lateral film at Baseline. Follow-up radiographs will be included in the long-term extension study for PD/efficacy documentation (first follow-up expected at age 2 years). Radiographs are the preferred imaging modality as they detect tooth bud mineralization but do not require sedation in the infant.

The sibling sub-study includes a dental examination that is brief and age-appropriate involving an assessment of tooth count and tooth shape. No X-ray exposure will be involved.

4.3 Genetic Testing

To meet inclusion criteria for EDI200 administration, potential study subjects are required to have their XLHED diagnosis confirmed by genetic testing of the EDA gene and these test results relayed to the study site. EDA genetic testing itself is outside of the scope of this protocol. If requested, the families of prospective subjects in need of EDA genotyping will be referred to resources available to facilitate this testing. Consent from the family (written or verbal) will be obtained as part of the screening process to provide the study site with documentation of genetic testing results via a secure and confidential method including an option for electronic transmission.

It has been demonstrated that a polymorphism in the EDAR gene associated with increased activity may be associated with amelioration of some XLHED-symptoms (Cluzeau et al., 2012). As this has the potential to impact outcome measures, all participating neonates will be tested for this specific polymorphism, c.1540T>C, rs3827760, p.V370A. The testing may be performed on the prior DNA sample used for EDA genotype confirmation, although results are not required prior to the initiation of dosing.

4.4 Digital Facial Photographs

A facial recognition software algorithm is under development that will identify characteristics of XLHED-affected neonates, children and adults. The algorithm uses non-invasive 2D frontal photographs and will be used in this study to document the newborn facial appearance as well as changes in craniofacial appearance over time, including the long-term extension study. Facial frontal and lateral digital images will be obtained with a commercial camera, and all photographs will be anonymized prior to transmission for analysis to FDNA, the company developing the software algorithm (http://www.fdna.com).

4.5 Clinical and Safety Laboratory Evaluations

4.5.1 *Safety Laboratory Sampling*

Laboratory parameters measured at the study site will include a complete blood count (RBC, WBC, hemoglobin and hematocrit) with differential and platelet count, serum chemistries including glucose, electrolytes (Na, K, Cl, Ca), total protein and albumin, assessment of hepatic and renal function (BUN, serum creatinine, AST, ALT and alkaline phosphatase), and urinalysis (dipstick and microscopy). It will be the Principal Investigator's responsibility to assess laboratory parameters against local reference ranges and to assess the clinical significance of any out-of-range values.

4.5.2 *Pharmacokinetic Sampling*

Analysis will be performed to characterize EDI200 PK after the doses designated as dose #1 and #5. Blood samples (0.25 ml) for determination of EDI200 in plasma will be taken into collection tubes without additives on the days and times indicated. The model used to determine frequency of pharmacokinetic sampling incorporates a sparse sampling approach in order to reduce the number of blood samples required for each subject. Note that additional PK samples are scheduled for age 2 and 6 months to assess study drug persistence at low levels as was reported for XLHED adults.

PK samples will be drawn at approximately the following time points pre-dose (defined as prior to the start of infusion) and post-dose (defined as after infusion is completed):

	Pre-Dose	Post-Dose							
		15 (±5) min	3 (±.5) hrs	8 (±1) hrs	18 (±2) hrs	24(±2) hrs	48 (±4) hrs	168(±8) hrs	Age 2 months (±1 wk) & 6 months (±2 wks)
D0 (dose 1)	X	X	X	X		X	X		
D14 (dose 5)	X	X	X		X		X	X	X

Immediately upon sampling, the sample will be identified with a label bearing details of the study number, subject number, sampling time point, and a sample type. The sample will be separated by centrifugation at rotation 1500xg, 4°C for 10 minutes. Two 50 ul aliquots of serum will be transferred to polypropylene tubes labeled identically to the original blood sample and stored at approximately -70°C pending analysis. The time at which samples are taken, received into the separating room and placed in the freezer will be recorded in the study documentation.

4.5.3 *Immunogenicity Sampling*

Blood samples (~0.25 mL per sample) for immunogenicity sampling will be taken into serum separator tubes on the days indicated.

Immediately upon sampling, the sample will be identified with a label bearing details of the study number, subject number, sampling time point, and a sample type. The sample will be separated by centrifugation. Two equal aliquots of serum will be transferred to polypropylene tubes labeled identically to the original blood sample and stored at approximately -70°C pending analysis. The calendar date and 24-hour clock time at which samples are taken, centrifuged and placed in the freezer will be recorded in the study documentation.

4.5.4 *Total of Blood Volume*

The approximate number of safety laboratory evaluations and the approximate volume of blood that will be collected per subject throughout the study are as follows:

All Subjects	Genetic Testing (5 ml)*	Safety Labs (1.5 ml)	Immunogenicity (0.25 ml)	PK (0.25 ml)	Total Blood Volume (ml)	ml/kg (3.5 kg neonate)
Screening	0	0	0	0	0.00	
Baseline	1 x 5 = 5.0	1 x 1.5 = 1.5	1 x 0.25 = 0.25	0	6.75	1.93
Week 1	0	1 x 1.5 = 1.5	0	6 x 0.25 = 1.50	3.00	0.86
Week 2	0	0	0	0	0	0
Week 3	0	1 x 1.5 = 1.5	1 x 0.25 = 0.25	5 x 0.25 = 1.25	3.00	0.86
Week 4	0	1 x 1.5 = 1.5	0	1 x 0.25 = 0.25	1.75	0.50
Months 2,4,6	0	2 x 1.5 = 3.0	2 x 0.25 = 0.50	2 x 0.25 = 0.50	4.00	
Total	1 x 5 = 5.0	6 x 1.5 = 9.0	4 x 0.25 = 1.0	13 x 0.25 = 3.25	18.25	

. For testing of the EDAR polymorphism in the case that DNA is not available from prior genotyping

4.6 Safety Evaluations

The safety evaluations will consist of adverse events, concomitant medications, vital signs, weight, physical exam findings, and safety laboratory values. Adverse events will be recorded starting when the treatment Informed Consent document (ICF2) is signed and continuing until all study assessments are completed (including Month 6 follow-up evaluations for all AEs, and Month 6 + 28 days for SAEs). Information on the definition, characteristics, and reporting requirements are provided below.

4.6.1 *Adverse Events*

4.6.1.1 Definition

An adverse event (AE) is any reaction, side effect, or other untoward event (signs, symptoms, or changes in laboratory data) associated with participation in this study, whether or not the event is considered related to the study or any of the procedures being conducted. All AEs occurring after signing the informed consent document will be recorded. AEs will be

ascertained on the basis of volunteered symptoms and clinical observation. AEs will be recorded during the study on the appropriate CRF page. All AEs considered to be related to study procedures, and all serious adverse events (SAEs; see Section 4.5.2) will be followed until resolved or until a stable status has been achieved. SAEs will be recorded up to 28 days following the Day 168 visit.

4.6.1.2 Reporting Adverse Events

Any adverse event (AE, a clinical sign, symptom, or disease) temporally associated with this study, whether or not considered related to study drug, shall be documented on the case report form (CRF). All AEs reported by the subject or observed by the PI will be individually listed. The signs and symptoms, the date of onset, duration, relationship to study drug, action taken, and follow-up procedures will be reported.

4.6.1.3 Relationship

The relationship between an AE and the administration of study drug or the procedures employed in this study will be determined by the PI on the basis of his or her clinical judgment and the following definitions:

Definitely Related: Follows a reasonable temporal sequence from administration of study drug; follows a known response pattern to the study procedure; and, when appropriate to the protocol, is confirmed by improvement after stopping the study procedure (positive re-challenge) and by reappearance of the reaction after repeat exposure (positive re-challenge); and cannot be reasonably explained by known characteristics of the participant's clinical state or by other therapies.

Probably Related: Follows a reasonable temporal sequence from administration of study drug; follows a known response pattern to the study procedure; and, when appropriate to the protocol, is confirmed by improvement after de-challenge; and cannot be reasonably explained by the known characteristics of the participant's clinical state or by other therapies.

Possibly Related: Follows a reasonable temporal sequence from administration of study drug and follows a known response pattern to the study procedure but could have been produced by the participant's clinical state or by other therapies.

Unlikely Related: The reaction has little or no temporal sequence from administration of the study drug, and/or a more likely alternative etiology exists.

Not Related: Sufficient information exists to indicate that the etiology is unrelated to administration of study drug in this study. Two or more of the following variables apply:

- The AE does not follow a reasonable temporal sequence with occurrence of administration of study drug;
- The AE is readily explained by the participant's clinical state or other therapies.

4.6.1.4 Severity

The intensity of an AE, as determined by the PI, will be assessed and graded utilizing a 5-point scale according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v4.0). It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under section 4.6.2. If a subject experiences the same AE with more than one level of intensity, the highest level of intensity should be recorded on the CRF. The severity grading will be reported in the eCRF as follows:

Grade 1 = **Mild;** asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 = **Moderate**; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
Grade 3 = **Severe** or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
Grade 4 = **Life-threatening** consequences; urgent intervention indicated.
Grade 5 = **Death** related to AE.

4.6.1.5 Outcome

The outcome of an AE will be assessed as follows:

- Resolved
- Unresolved
- Resolved with sequelae
- Death
- Unknown

4.6.2 *Serious Adverse Event*

4.6.2.1 Serious Adverse Event Definition

An SAE is any AE that results in any of the following outcomes:
- Death
- A life threatening AE

  - The term "life-threatening" means that the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe
- An inpatient hospitalization or prolongation of existing hospitalization (24 hours or more)
- A persistent disability/incapacity, or a
- A congenital anomaly/birth defect
- Important medical event

An important medical event may not result in death, be life threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

4.6.2.2 Serious Adverse Event Reporting

The PI will report all SAEs to the Sponsor in a timely fashion, within 24 hours of awareness, by completing and faxing the SAE Report Form to CTI Safety as per directions described in the Study Reference Manual. The reporting PI is obligated to provide their initial assessment of the relationship between study drug and the occurrence of each SAE. Determination of expectedness and the reporting of the SAEs to relevant regulatory authorities will be determined by the Sponsor. The reporting PI is responsible for reporting all SAEs to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) as required by the appropriate regulations.

Based on the investigator's assessment of causality of the adverse event and discussions with the medical monitor, a decision will be made by the sponsor concerning the need for further action with respect to the future conduct of this trial. The primary consideration governing further action is whether new findings affect the safety of other subjects participating in the clinical study. If the discovery of a new adverse event related to study drug raises concerns over the safety of its continued administration to subjects, the sponsor or designee will take immediate steps to notify the Data Safety Monitoring Board (DSMB), the regulatory authorities and all the investigators participating in clinical studies of the study drug.

The Sponsor will notify the relevant regulatory authorities according to Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) regulations. The reporting PI will notify the Sponsor through the following contact:

Name:	CTI Global Drug Safety & Pharmacovigilance
Address:	10123 Alliance Road Cincinnati, OH 45242
Telephone:	1-877-755-0742
Fax:	1-866-215-5862
E-mail:	CTISafety@ctifacts.com

Additional SAE follow-up information, if required, should all be faxed to CTI Safety within 24 hours of receipt. The follow-up information should be documented on the original SAE Report Form following Good Documentation Practices and faxed with any additional relevant source documentation. Additionally, the AE eCRF should be updated accordingly to match the SAE Report form.

SAE source documentation requested may include; discharge summary, diagnostic test results, consultation reports, relevant specimen cultures, diagnostics, or laboratory values. The investigator must ensure that all source documentation maintains each subject's anonymity. The site and subject number must be documented on every page, the subject's name replaced by the subject's study number, and all other protected health information should be redacted (e.g. social security number, medical record number, room number, etc.).

Compliance with the requirements for expedited reporting is essential. The sponsor or the sponsor's designee is responsible for informing the regulatory authorities as well as all other participating investigators of the following events:

- Any event associated with the use of the study drug, that is both serious and unexpected (SUSAR), or
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.

The sponsor or designee will expedite the reporting of all SUSARs to the appropriate regulatory authorities and the Institutional Review Board/Independent Ethics committee (IRB/IEC). The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse event (AE). For fatal or life threatening cases, the term will be a maximum of 7 calendar days for a preliminary report with another 8 calendar days for completion of the report. The sponsor or designee will also inform all investigators of such events.

The sponsor or designee will provide expedited reports of the following SUSARs to the IRB/IEC:

- SUSARs that have arisen in the clinical trial that were assessed by the EC
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that were assessed by the EC.

4.7 Concomitant Medication

There are no concomitant medications that are excluded from this study. There are no concomitant medications known to interact with EDI200.

4.8 Data Safety Monitoring Board (DSMB)

An independent DSMB will be established to monitor the safety of treated subjects. A European member has been added to the same DSMB in place for the Phase 1 adult safety study (ECP-004) to monitor this neonate trial. All safety-related laboratory values will be available to the DSMB in real time. At the scheduled DSMB review meetings, detailed safety reviews will be provided to the DSMB including; adverse events, concomitant medications, infusion/injection site reactions, physical examination, weights and vital signs, and all PK and safety laboratory values. Scheduled DSMB meetings include the following:

- After dosing is completed in XLHED neonate cohort 1, the DSMB will meet and review safety and PK data from all cohort 1 subjects prior to initiation of dosing in XLHED neonate cohort 2. The timeframe for this review is approximately three weeks following dosing of the last cohort 1 subject. The cohort 1 PK data review is intended to confirm that the exposure levels in the cohort as a whole and for each subject were within the limits associated with safe study drug administration in the preclinical GLP toxicology studies, and that the expected exposure with dose escalation in cohort 2 will remain in the range that was safe and well tolerated. Additionally, the DSMB will review safety and PK data obtained from adult cohort 2 (NCT01564225, www.clinicaltrials.gov) dosed at the same 10 mg/kg/dose as is proposed for neonate cohort 2.
- At the end of the Study, DSMB will review and summarize all study safety data. DSMB summaries will be provided in a timely fashion to the Sponsor.

Unscheduled DSMB reviews will take place as outlined in Section 3.3.4-3.3.7 for single or accumulated adverse events. Additional safety-related evaluations of one or more subjects may be requested by the DSMB based on findings through the 6-month, end-of-study visit.

5 SCHEDULE OF STUDY ASSESSMENTS

5.1 Screening – End of first trimester through DOL #12

- Medical history related to XLHED in the family and for pregnancy, labor and delivery
- Verbal consent from both parents (if reasonably available) to provide documentation of genetic testing results to the study site by a secure and confidential method including the option for electronic transmission
- Inclusion/Exclusion criteria will be confirmed for parents and fetus/neonate

**A screening call may be conducted to assess eligibility for study participation, inclusion/ exclusion criteria, and availability of EDA genetic test results. If prior genotyping is not available, either cord blood or a neonatal blood sample may be sent to an accredited laboratory for testing.*

5.2 Baseline – DOL #2 through DOL #14

- Transport Informed Consent from both parents (if reasonably available) if neonatal transport to the study site is to be provided as part of the study
- Treatment Informed Consent from both parents (if reasonably available) for study procedures and study drug administration
- Confirmation of inclusion/exclusion criteria
- Updated medical history
- Full physical examination
- Blood draws for safety laboratories, EDAR gene V370A polymorphism testing, PK and immunogenicity
- Bioactivity assessments
    - Growth and development
    - Dental imaging
    - Digital facial photograph
    - Sweat duct density (males only)
    - Sweat rate (males only)
    - Dry eye assessment
    - Thermoregulation
    - Skin biopsy sample for molecular profiling (males only)
- Adverse Events & Concomitant Medications

5.3 Treatment

Day 0

- Brief physical exam (prior to dosing)
- Study drug administration (dose 1)
- Vital sign monitoring during and for 24 hours following study drug infusion
- Blood draw for PK analysis at the following timepoints:
    - Post-end of infusion timepoints: 15 min, 3 and 8 hours
- Adverse Events & Concomitant Medications

Day 1

- Brief physical exam
- Blood draw for safety laboratory evaluations
- Blood draw for PK analysis at the following timepoints:
    - 24 hours post dose 1
- Skin biopsy 24 hours post dose 1 (males only)
- Adverse Events & Concomitant Medications

Day 2

- Blood draw for PK analysis at the following timepoints:
    - 48 hours post dose 1
- Adverse Events & Concomitant Medications

Day 4

- Brief physical exam (prior to dosing)
- Study drug administration (dose 2)
- Vital sign monitoring during and for 24 hours following study drug infusion
- Adverse Events & Concomitant Medications

Day 7

- Brief physical exam (prior to dosing)
- Study drug administration (dose 3)
- Vital sign monitoring during and for 24 hours following study drug infusion
- Adverse Events & Concomitant Medications

Day 11

- Brief physical exam (prior to dosing)
- Study drug administration (dose 4)
- Vital sign monitoring during and for 24 hours following study drug infusion
- Adverse Events & Concomitant Medications

Day 14

- Brief physical exam (prior to dosing)
- Study drug administration (dose 5)
- Vital sign monitoring during and for 24 hours following study drug infusion
- Blood draws for PK analysis at the following timepoints:
    - Pre-dose and the following post-end of infusion timepoints: 15 minutes, 3 and 18 hours
- Adverse Events & Concomitant Medications

Day 15

- Brief physical exam
- Skin biopsy (males only) for molecular profiling (24 hours after study drug administration)
- Adverse Events & Concomitant Medications

Day 16

- Blood draw for PK analysis at the following timepoints:
    - 48 hours post dose 5
- Blood draw for safety laboratory evaluations
- Blood draw for immunogenicity testing
- Adverse Events & Concomitant Medications

Day 21

- Full physical exam
- Blood draw for safety laboratory evaluations
- Blood draw for PK analysis at the following timepoints:
    - 168 hours post dose 5
- Thermoregulation assessment
- Adverse Events & Concomitant Medications

**If any visits are adjusted during the baseline and/or treatment portions of the study (if a subject is seen or dosed earlier or later than what is described in the protocol) then all subsequent visits (if applicable) should be adjusted accordingly.*

5.4 Post-Treatment

Follow-Up Visit 1 – Month of Life 2 (±1 week)

- Full physical exam
- Blood draw for safety laboratory evaluations
- Blood draw for immunogenicity testing
- Blood draw for PK
- PD/efficacy assessments

  - Growth and development
  - Sweat rate (males only)
- Adverse Events & Concomitant Medications

Follow-Up Visit 2 – Month of Life 4 (±1 week)

- Full physical exam
- PD/efficacy assessments
  - Growth and development
- Adverse Events & Concomitant Medications

End-of-Study Visit – Month of Life 6 (±2 weeks)

- Full physical exam
- Blood draw for safety laboratory evaluations
- Blood draw for immunogenicity testing
- Blood draw for PK
- PD assessments
  - Growth and development
  - Digital facial photographs
  - Sweat duct density (males only)
  - Sweat rate (males only)
  - Dry eye assessments
- Adverse Events & Concomitant Medications

5.5 Unscheduled Visits

The Sponsor or DSMB may request unscheduled visits either during the subject's participation in the Study or after his/her completion. The unscheduled visits may include additional safety-related evaluations (including blood sampling) based on findings through the 6-month, end-of-study visit.

6 STATISTICAL METHODS

6.1 Sample Size

The sample size is based on clinical and practical considerations for a Phase 2 study in an ultra-rare genetic disorder with enrollment limited to newborns. It is considered to be appropriate to meet the objectives of the study while minimizing the exposure of volunteers. Each cohort is anticipated to enroll approximately 3-7 XLHED-affected neonates. No more than 10 subjects total will be enrolled.

6.2 Analysis Datasets

The safety analysis set will consist of all subjects who receive at least one dose of study medication. The PK analysis set will consist of those subjects who receive at least one dose of study medication and have sufficient concentration data to obtain a plasma concentration by time profile. The PD/efficacy analysis set will consist of all subjects who receive at least one dose of study medication and complete the follow-up assessments through at least month 2. No missing data will be replaced by values carried forward.

6.3 Primary and Pharmacodynamic/Efficacy Assessments

The safety assessment variables are AEs, concomitant medications, vital signs, weight, physical examination findings, hematology, clinical chemistry, and urinalysis laboratory test results.

The PK assessment variables will be the following derived PK parameters for EDI200:

- C_{max}, T_{max}, $AUC_{0\text{-}tau}$
- Other PK parameters including but not limited to clearance rate may also be examined.

The medical history and clinical evaluations for the sibling sub-study will be tabulated and intra-familial comparisons will be made with data obtained from the neonate subjects receiving study drug.

The following pharmacodynamic/efficacy outcomes will be monitored in all subjects receiving study drug:

- Growth and development
- Dentition (follow-up radiographs in extension study)
- Craniofacial development by digital photography
- Sweat duct density (males only)
- Sweat rate (males only)
- Dry eye signs and symptoms
- Thermoregulation
- Molecular expression profile of skin biopsy tissue (males only)

6.4 Pharmacodynamic/Efficacy Variables (not including sibling sub-study)

Growth and Development:
Testing to be performed at Baseline, Months of Life 2, 4, 6:

- Weight, length, head circumference plotted on standardized growth curves for newborns
- Developmental assessments

Dental Imaging:
Testing to be performed at Baseline:

- Lateral jaw film

Craniofacial Development:
Testing to be performed at Baseline, Month of Life 6

- Digital facial photographs

Sweat Duct Density (males only):
Testing to be performed at Baseline, Month 6:

- Sweat ducts per 36 mm^2 on confocal microscopy image

Sweat Rate (males only):
Testing to be performed at Baseline, Months of Life 2 and 6:

- Volume of induced sweat collected over 30 minutes following pilocarpine iontophoresis

Dry Eye Assessments:
Testing to be performed at Baseline, Month 6:

- Examination for signs of infection and/or irritation, as well as tear film break-up time

Thermoregulation:
Testing to be performed at Baseline, TD21:

- Clinical and vital sign response to isolette temperature range

Skin Biopsy for Molecular Expression Profile (males only):
Testing to be performed at Baseline, TD1 (approximately 24 hours after 1st dose) and TD15 (approximately 24 hours after last dose):

- Analysis of gene expression on skin biopsy samples

6.5 Analysis of Safety and Pharmacokinetic Variables

Safety variables will be tabulated and presented for all subjects receiving one or more doses of EDI200. Change from Baseline over time will be presented by cohort for continuous variables including laboratory values and vital signs using descriptive statistics with n, mean, standard

deviation, minimum, median and maximum as appropriate. Shift tables will be presented. Out-of-range values will be flagged in the data listings and will also be presented separately.

AEs will be coded using the current MedDRA drug dictionary version. Only treatment emergent AEs will be included in the summary tables. The incidence of subjects reporting AEs will be summarized by system organ class, preferred term, severity and relationship to study drug.

The PK parameters of EDI200 will be listed and summarized by dosing cohort. Mean and individual plasma concentration-time curves will be presented on both linear and semi-logarithmic scales. The derivation of the PK variables from the EDI200 plasma concentrations will be determined using WinNonlin Professional v5.2, or higher. The PK parameters of EDI200 will be listed and summarized.

6.6 Statistical Methods

Individual subject values for EDA genotype and all endpoints, both at Baseline and across time, will be provided. Demographics for the entire study dataset will be presented using descriptive statistics. Table summaries of Baseline values for all endpoints will be provided for the following groups: all subjects and each dosing cohort. Descriptive statistics will be provided across time for each cohort with n, mean, standard deviation, minimum, median and maximum as appropriate.

6.7 Data Management

As outlined in section 7.5 the Sponsor or designee will forward questions regarding missing data or discrepancies to the PI.

The original terms used in the case report forms by the PI to identify adverse events will be coded according to the MedDRA dictionary. The percentage of subjects with adverse events will be tabulated overall and by the MedDRA body system and preferred term.

7 STUDY ADMINISTRATION

7.1 Protocol Modifications

Neither the PI nor Sponsor will modify this protocol without obtaining the concurrence of the other. All protocol amendments must be issued by the Sponsor, signed and dated by the PI, and should not be implemented without prior IRB/IEC approval, except where necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study (e.g., typographical errors, inconsistencies).

In situations requiring a departure from the protocol, the PI or other physician in attendance will discuss with the appropriate Sponsor representative. This contact will be made before implementing any departure from protocol. In all cases, contact with the Sponsor will be made as soon as possible in order to discuss the situation and agree on an appropriate course of action. Any departure from the protocol and the circumstances requiring it will be documented.

7.2 Monitoring

The Sponsor or their designee (hereby referred to as “Monitor”) will monitor all aspects of the study as required by GCP and any existing standard operating procedures for compliance with applicable regulations. These individuals will have access to all records necessary to ensure integrity of the data and will review progress of the study with the PI.

The monitor will compare the data entered into the CRF’s with any source documents. The nature and location of any source documents will be identified in advance. This will ensure that all sources of original data required to complete the CRF are known to the Sponsor and investigational staff; and are accessible for verification by the Monitor. If electronic records are maintained, the method of verification must be discussed with the investigational staff. At a minimum, source documentation must be available to substantiate subject identification, eligibility and participation, proper informed consent procedures, adherence to protocol procedures, record of safety parameters, adequate reporting and follow-up of adverse events, completion and reason of withdrawal/ termination. Specific items required as source documents will be reviewed with the PI before the study. The author of an entry in the source documents will be identifiable.

If any data are recorded directly into the CRF, at a minimum there should be an entry in the source document that each of the assessments was done, and by whom and the date it was done. The author of an entry in the source documents must be identifiable. The CRF data will be entered into an appropriate data storage system and verified for accuracy.

Direct access to source documentation must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. Findings from this review

of CRF's and source documents will be discussed with the investigational staff. The Sponsor expects that, during monitoring visit(s), the relevant investigational staff will be available, the source documentation will be available, and a suitable environment will be provided for review of study-related documents. The monitor will provide feedback on the study conduct to the PI.

The investigator will permit trial-related monitoring, audits, audits, IRB/IEC review, and regulatory inspection(s), and providing direct access to source data/documents.

7.3 Ethic Aspects

7.3.1 PI Responsibilities

The PI is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines, Good Clinical Practice (GCP), and applicable regulatory requirements.

GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well being of study subjects are protected, consistent with the principles that have originated in the Declaration of Helsinki and that the clinical study data are credible.

7.3.2 Institutional Review Board/Independent Ethics Committee

The PI will provide the Institutional Review Board/Independent Ethics committee (IRB/IEC) with all requisite material, including a copy of the protocol, informed consent and all subject materials. The study will not be initiated until the IRB/IEC provides written approval of the protocol and the informed consent and the PI has obtained documents approved by the IRB/IEC. Any reports requested on the progress of this study by the PI will be made to the IRB/IEC and the Sponsor.

7.3.3 Informed Consent

A properly executed, written informed consent in compliance with national and local regulations and GCP guidelines will be obtained from each subject prior to entering the study or performing any study-related procedure.

The PI will submit a copy of the informed consent document to the IRB/EC for review and approval before research subjects are enrolled. The PI will provide a version of the signed informed consent to the subject and a signed version will be maintained in the subject's research record.

7.3.4 Confidentiality of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the safety, quality, and utility of the procedures performed during this study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

The Sponsor ensures that the personal data are:

- Processed fairly and lawfully
- Collected for specified, explicit, and legitimate purposes and not further processed in a way incompatible with these purposes
- Adequate, relevant, and not excessive in relation to said purposes
- Accurate and, where necessary, kept up to date

Explicit consent for the processing of personal data will be obtained from the participating subject before collection of data. Such consent should also address the transfer of the data to other entities and to other countries, if applicable.

The subject has the right to request through the PI access to his/her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps should be taken to respond to such request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel and designees whose responsibilities require access to personal data agree to keep the identity of study subjects confidential.

7.4 Subject Identification Register

The PI agrees to complete a subject identification register to permit easy identification of each subject during and after the study. The Monitor will review the document for completeness.

The subject identification register will be treated as confidential and will be filed by the PI in the Regulatory Binder. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by initials and assigned number only.

7.5 Case Report Form Completion

All of the clinical data will be captured via electronic data capture (EDC) using an approved and validated EDC system. The investigator site staff will enter and edit the data via a secure network, with secure access features (username, password and secure identification – an electronic password system). A complete electronic audit trail will be maintained.

The investigator will approve the data using an electronic signature, and this approval is used to confirm the accuracy of the data recorded (CFR 21, Part. 11, 2011).

Electronic CRF's (eCRF) will be used for all patients. The investigator's data will be accessible from the investigator's site throughout the trial. The eCRFs must be kept current to reflect patient status at each phase during the course of the trial. The patients must not be identified on the eCRF by name. The appropriate coded identification (i.e. Patient Number) must be used. The investigator must make a separate confidential record of these details (subject identification record) to permit identification of all patients enrolled in a clinical trial in case follow-up is required.

Copies of the eCRF together with all data changes made will be supplied to the investigator at the end of the trial. The investigator will be responsible for retaining all records pertaining to the trial as specified in the appropriate contract.

7.6 Data Quality Assurance

Steps to be taken to assure the accuracy and reliability of data include the selection of a qualified PI, review of protocol procedures with the PI and associated personnel before the study, and a monitoring visit(s) by the Sponsor. Instruction for completion of CRFs will be provided and reviewed with study personnel before the start of the study. The Monitor will review CRFs for accuracy and completeness during the conference and/or during a monitoring visit(s). Any discrepancies will be resolved with the PI or designee, as appropriate. The data will be entered into an appropriate data storage system and verified for accuracy.

7.7 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

APPENDIX 1 – AUTOMATIC PHENOTYPE IDENTIFICATION OF XLHED PATIENTS

FINAL REPORT

Provided as a separate document.

APPENDIX 2 – THE NATIONAL CANCER INSTITUTE (NCI) COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS V4.0 (CTCAE)

VERSION 4.0

US DEPARTMENT OF HEALTH AND HUMAN SERVICES- NATIONAL INSTITUTES OF HEALTH-NATIONAL CANCER INSTITUTE

Provided as a separate document.

APPENDIX 3 – MEDICAL QUESTIONNAIRE FOR MOTHERS AND XLHED-AFFECTED NEONATES

Medical Questionnaire for Mothers and XLHED-Affected Neonates

Participant's Initials: ☐☐☐ **Can be left blank if choice of name is not yet finalized*

Today's Date: ☐☐/☐☐/☐☐☐☐

Date of birth: ☐☐/☐☐/☐☐☐☐
DD/MM/YYYY

Has the mother been diagnosed with HED? ☐Yes ☐No

If yes, age at diagnosis: ☐0-5 years ☐6-17 years ☐≥18 years

Does the mother have any family members diagnosed with HED? ☐Yes ☐No

If yes, check all that apply:
☐Mother
☐Father
☐Sisters
☐Brothers
☐Aunts
☐Uncles
☐Other
If other, specify:

Has the mother or any family member(s) had genetic testing for HED? ☐Yes ☐No
**Every attempt should be made to obtain a copy of the genetic test results. The results must be provided to the study site and will also be provided to the lab conducting your baby's genetic testing in order to expedite the testing process.*

Mother's age at delivery: ☐☐

What number pregnancy is/was this child for the mother? ☐☐

Is the mother currently pregnant? ☐Yes ☐No

Thinking of *all* of the mother's pregnancies to date, including this one, how many resulted in each of the following:

	Number
Miscarriage in the first trimester (up to 14th week of pregnancy)	☐☐
Miscarriage later in pregnancy	☐☐
Stillbirth	☐☐
Preterm birth (prior to 37 weeks)	☐☐
Full term birth (37 weeks or more)	☐☐

Did the mother have any of the following complication during ***this child's*** (the study subject) pregnancy? ☐Yes ☐No

If yes, please list treatment.

Diabetes: _____
High blood pressure: _____
Infections, fevers and illnesses: _____
Other problems/complications: _____

Medications used during pregnancy: _____
_____
Are any of these medications investigational? ☐Yes ☐No

Did the mother have any of the following?
☐Ultrasound
☐1st trimester screen/triple/quad screen
☐Amniocentesis or CVS

Were any results from this testing abnormal? ☐Yes ☐No

If yes, please explain:
_____
_____

Check here ☐ if your child is not born yet and do NOT complete the rest of this form.

The child was born:
☐Full-term
☐Prematurely (weeks premature: ☐☐)

If premature, please list the reason:
_____

The child was born: ☐Vaginally ☐By C-section
If by C-section, why: _____

Birth Hospital: _____

Birth location:

Country: _____
City: _____
State (if applicable): _____

Birth weight: ☐☐.☐☐ kg
Birth Length: ☐☐☐ . ☐☐cm
Birth head circumference: ☐☐☐ . ☐☐cm

Did your child have any problems after delivery or require admission to the Neonatal Intensive Care Unit (NICU)? ☐Yes ☐No

If yes, please explain:

_____

_____

Did he/she pass the:
Newborn metabolic screen: ☐Yes ☐No ☐Unsure
Newborn hearing screen: ☐Yes ☐No ☐Unsure

How many days old was child when he/she went home from the hospital? ☐☐

Did the child have any other problems in the first few days of life? ☐Yes ☐No
If yes, please explain: _____

_____

APPENDIX 4 – MEDICAL QUESTIONNAIRE FOR SIBLINGS OF STUDY SUBJECTS

Medical Questionnaire for Siblings of Study Subjects

*One questionnaire to be completed by each male sibling

Participant's Initials: ☐☐☐

Participant's ID #: ☐☐☐
*To be completed by study personnel

Gender: ☐Male ☐Female

Today's Date: ☐☐/☐☐/☐☐☐☐

Date of birth: ☐☐/☐☐/☐☐☐☐
DD/MM/YYYY

Are you currently experiencing any major medical problems that would prevent you from participating in this study? ☐Yes ☐No

Do you have a known hypersensitivity to pilocarpine or pilocarpine-like muscarinic agonists (Examples: Urecholine, Salagen, Pilocar, and Provocholine)? ☐Yes ☐No

Do you have a pacemaker? ☐Yes ☐No

Have you been diagnosed with HED? ☐Yes ☐No

If yes, age at diagnosis: ☐0-5 years ☐6-17 years ☐≥18 years

Do you have any family members diagnosed with HED? ☐Yes ☐No

If yes, check all that apply:
☐Mother
☐Father
☐Sisters
☐Brothers
☐Aunts
☐Uncles
☐Other

If other, specify:

Have you or any family member(s) had genetic testing for HED? ☐Yes ☐No

Do you know the genetic test results? ☐Yes ☐No

Have you ever been referred to any of the following types of physicians?

Dermatologist	☐Yes	☐No
Pediatric dermatologist	☐Yes	☐No
Geneticist	☐Yes	☐No
Genetic counselor	☐Yes	☐No
Dentist	☐Yes	☐No
Pediatric dentist	☐Yes	☐No

Do you have decreased sweating?	☐Yes ☐No
Do you sweat on certain parts of your body?	☐Yes ☐No
If so, from what body part(s) do you sweat and at what age did you notice you started sweating in that area?	
Body Part: ____________ Age you noticed:	☐0-5 yrs ☐11-17 yrs ☐6-10 yrs ☐>18 yrs
Body Part: ____________ Age you noticed:	☐0-5 yrs ☐11-17 yrs ☐6-10 yrs ☐>18 yrs
Body Part: ____________ Age you noticed:	☐0-5 yrs ☐11-17 yrs ☐6-10 yrs ☐>18 yrs
Body Part: ____________ Age you noticed:	☐0-5 yrs ☐11-17 yrs ☐6-10 yrs ☐>18 yrs
Body Part: ____________ Age you noticed:	☐0-5 yrs ☐11-17 yrs ☐6-10 yrs ☐>18 yrs
Body Part: ____________ Age you noticed:	☐0-5 yrs ☐11-17 yrs ☐6-10 yrs ☐>18 yrs
Do you have unexplained fevers?	☐Yes ☐No
Did you ever suffer from seizures associated with fever?	☐Yes ☐No
Do you suffer from heat intolerance?	☐Yes ☐No
Is your exercising limited by heat intolerance?	☐Yes ☐No

Does your decreased sweating/heat intolerance affect your: **Check all that apply*	☐Daily life ☐Choice of occupation ☐Involvement in indoor sports ☐Involvement in outdoor sports ☐Decision to live in cooler climate ☐Choice of vacation destinations ☐Ability to travel

Have you experienced hair or eyebrow thinning or scalp hair loss?	☐Yes ☐No
If yes, what age were you when you noticed the loss of hair?	☐0-5 yrs ☐6-10 yrs ☐11-17 yrs ☐>18 yrs
How often do you get your hair cut?	☐Daily ☐Weekly ☐Monthly ☐Yearly
Do you get haircuts less often than unaffected siblings/ classmates?	☐Yes ☐No
Have you ever tried a topical treatment to reduce hair thinning?	☐Yes ☐No

Do you have problems with your teeth (no teeth, missing or misshapen teeth)?			☐Yes ☐No
If yes, describe age of treatment with dentures and/or implants if applicable (check all that apply):		Dentures	Implants
	1-5 years	☐	☐
	6-10 years	☐	☐
	11-17 years	☐	☐
	≥18 years	☐	☐
To the best of your knowledge how many baby teeth did you develop?			☐☐
To the best of your knowledge how many adult teeth did you develop?			☐☐
Do you suffer from dry mouth?			☐Yes ☐No
Do you suffer from dry eyes?			☐Yes ☐No
Do you require eye drops on a regular basis?			☐Yes ☐No
Do you suffer from frequent eye infections?			☐Yes ☐No

Did you have chronic nasal drainage/blockage as a child?		☐Yes ☐No
Did you suffer from nosebleeds as a child?		☐Yes ☐No
If yes, at what age did you first notice them?	☐0-5 yrs ☐6-10 yrs	☐11-17 yrs ☐≥18 yrs
Do you still experience nosebleeds?		☐Yes ☐No
How many times per year do you have nosebleeds?	☐☐	
Did you have respiratory related problems as a child?		☐Yes ☐No
If yes, were you ever hospitalized for antibiotic therapy?		☐Yes ☐No
Do you suffer from sinus infections most years?		☐Yes ☐No
If so, at what age did these sinus infections start?	☐0-5 yrs ☐6-10 yrs	☐11-17 yrs ☐≥18 yrs
Do you suffer from asthma?		☐Yes ☐No
If so, do you require medication to manage your asthma?		☐Yes ☐No
Do you experience a hoarseness of your voice?		☐Yes ☐No
If yes, at what age did you first notice it?		☐Yes ☐No
Is the hoarseness worse during the cold months?		☐Yes ☐No

Do you have problems with dry skin?	☐Yes ☐No
Have you ever had a diagnosis of eczema or atopic dermatitis?	☐Yes ☐No
If yes, have you tried prescription medications?	☐Yes ☐No

If yes, list medications:

Do you have a family history of eczema (other than XLHED family members)? ☐Yes ☐No

Hypohidrosis Severity 5-Point Likert Scale

1	2	3	4	5
Sweat as much as people without ED	Sweat a little less than people without ED (no problems in hot weather)	Some problems in sweating (sometimes have problems in hot weather)	A little sweating (I have problems in hot weather	No sweating at all (I have problems in hot weather)

Alopecia (hair loss or thinning) Severity 5-Point Likert Scale

1	2	3	4	5
Normal hair	Mild (<25%) hair loss	Moderate (25-75%) hair loss	Severe (>75%) hair loss	No hair

APPENDIX 5 – OCULAR SURFACE DISEASE INDEX© (OSDI©)

Provided as a separate document.

REFERENCES

A Phase 1, open label, multicenter, safety and pharmacokinetic study of EDI200, an ectodysplasin-A1 replacement molecule in X-Linked Hypohidrotic Ectodermal Dysplasia (XLHED) adults (ECP-004). Clinical Study Report. Edimer Pharmaceuticals, Inc.

Black, MM, Matula K. 2000. *Essentials of Bayley Scales of Infant Development-II Assessment*. New York, J Wiley & Sons, Inc.

Blüschke G, Nusken KD, Schneider H. 2010. Prevalence and prevention of severe complications of hypohidrotic ectodermal dysplasia in infancy. *Early Hum Dev*. 86: 397-9.

Casal M, Lewis J, Mauldin E, Tardivel A, Ingold K, Favre M, Paradies F, Demotz S, Gaide O, Schneider P. 2007. Significant Correction of Disease after Postnatal Administration of Recombinant Ectodysplasin A in Canine X-Linked Ectodermal Dysplasia. *Am J Hum Genet*. 81: 1050-1056.

Chawla, D, Agarwal R, Deorari A, Paul, V. 2008. Fluid and electrolyte management in term and preterm neonates. NICU Protocol. Division of Neonatology, Department of Pediatrics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi.

Clarke A, Sarfarazi M, Thomas NS, Roberts K, Harper PS. 1987. X-linked hypohidrotic ectodermal dysplasia: DNA probe linkage analysis and gene localization. *Hum Genet.* 75(4): 378-80.

Cloherty JP, Eichenwald EC, Stark AR. 2004. Manual of Neonatal Care (Fifth Ed). Philadelphia, PA: Lippincott, Williams & Wilkins.

Cluzeau C, Hadj-Rabia S, Bal E, Clauss F, Munnich A, Bodemer C, Headon D, Smahi A. 2012. The EDAR370A allele attenuates the severity of hypohidrotic ectodermal dysplasia caused by EDA gene mutation. *Br J Dermatol* 166:678-81.

Dietz J, Kaercher T, Schneider AT, Zimmerman T, Huttner K, Johnson R, Schneider H. 2013 Apr 4. Early respiratory and ocular involvement in X-linked hypohidrotic ectodermal dysplasia. *Eur J Pediatr* Epub ahead of print.

Ectodysplasin A (Fc:EDA1 aka EDI200) Replacement Therapy In A Canine Model Of Ectodermal Dysplasia: Pharmacological Assessment (NCD-200-11-005). Edimer Pharmaceuticals, Inc.

EDI200: A 3-Week Intraperitoneal/Intravenous Toxicity Study in Juvenile Dogs with a 2-Week Recovery Period (1800-010). Edimer Pharmaceuticals, Inc.

EDI200: A 3-Week Intraperitoneal Toxicity Study in Juvenile Mice with a 2-Week Recovery Period (1800-009). Edimer Pharmaceuticals, Inc.

"Electronic Records: Electronic Signatures." *Code of Federal Regulations* Title 21, Pt. 11, 2011 ed.

Fete M, Hermann J, Behrens J, Huttner K. 2014. X-Linked Hypohidrotic Ectodermal Dysplasia (XLHED): Clinical and Diagnostic Insights from an International Patient Registry. *Am J Med Genet A.* 9999: 1-6.

Gaide O, Schneider P. 2003. Permanent Correction of an Inherited Ectodermal Dysplasia with Recombinant EDA. *Nat Med*. 9: 614-618.

Haycock, G. B., Schwartz, G. J., & Wisotsky, D. H. 1978. Geometric method for measuring body surface area: a height-weight formula validated in infants, children, and adults. *J Pediatr*. 93(1), 62-6.

Hey E. 1975. Thermal neutrality. *British Med Bull*. *31*(1): 69-74.

Huttner K, Grange D, Klein O, Schneider H. 2012, February. Genotype/phenotype correlations in XLHED: Insights into the biology of ectodysplasin. Poster session presented at the 2012 Dermatogenetics Conference. Miami, Florida.

Itoh H, Uebori S, Asai M, Kashiwaya T, Atoh K, Makino I. 2003. Early Detection of Orthostatic Hypotension by Quantitative Sudomotor Axon Reflex Test (QSART) in Type 2 Diabetic Patients. *Internal Med*. 42: 560-564.

Lindfors P, Voutilained M, Mikkola M. 2013. Ectodysplasin/NF-κB Signaling in Embryonic Mammary Gland Development. *J Mammary Gland Biol Neoplasia.* 18: 165-169.

Low P, Caskey P, Tuck R, Fealey R, Dyck P. 1983. Quantitative Sudomotor Axon Reflex Test in Normal and Neuropathic Subjects. *Ann Neurol*. 14: 573-580.

Mastella G, Di Cesare G, Borruso A, Menin L, Zanolla L. 2000. Reliability of sweat testing by the Macroduct collection method combined with conductivity analysis in comparison with the classic Gibson and Cooke technique. *Acta Paediatrica. 89*(8): 933-7.

Mauldin E, Gaide O, Schneider P, Casal M. 2009. Neonatal Treatment with Recombinant Ectodysplasin Prevents Respiratory Disease in Dogs with X-Linked Ectodermal Dysplasia. *Am J Med Genet A.* 149A: 2045-2049.

Miller, R. 2003. Marginal Transfer of ReoPro™ (Abciximab) Compared with Immunoglobulin G (F105), Inulin and Water in the Perfused Human Placenta In Vitro. *Placenta*. *24*(7): 727-738.

Motil KJ, Fete TJ, Fraley JK, Schultz RJ, Foy TM, Ochs U, et al. 2005. Growth Characteristics Of Children With Ectodermal Dysplasia Syndromes. *Pediatrics*. 116(2): 229-34.

Ramaswami U, Wendt S, Pintos-Morell G, Parini R, Whybra C, Leon Leal J, Santus F, Beck M. 2007. Enzyme Replacement Therapy with Agalsidase Alfa in Children with Fabry Disease. *Acta Paediatr*. 96: 122-127.

Rutter N, Hull D. 1979. Response of term babies to a warm environment. *Arch Dis Child. 54*(3): 178-183.

Seeliger F, Drögemüller C, Tegtmeier P, Baumgärtner W, Distl O, & Leeb T. 2005. Ectodysplasin-1 deficiency in a German Holstein bull associated with loss of respiratory mucous glands and chronic rhinotracheitis. *J Comp Pathol*. 132(4): 346-9.

Sjörs G, Hammarlund K, Sedin, G. 1997. Thermal balance in term and preterm newborn infants nursed in an incubator equipped with a radiant heat source. *Acta Paediatrica. 86*(4): 403-9.

Stothers J K, Warner R M. 1984. Thermal balance and sleep state in the newborn. *Early Hum Dev*. *9*(4): 313-22.

Sulyok E, Jequier E, Prod'hom L. 1976. Relationship between body size, thermal balance and thermal insulation of term infants under various ambient conditions. *Biol Neonate*. *28*: 42-56.

Sweat Duct Imaging in Mother/Newborn Dyads (ECP-005). Clinical Study Report. Edimer Pharmaceuticals, Inc.

Swischuk, L. 2003. Imaging of the Newborn, Infant and Young Child (Fifth). Philadelphia, PA: Lippincott, Williams and Wilkins.

The Effect of Ectodysplasin A (Fc: EDA1) Replacement Therapy in a Canine Model of Ectodermal Dysplasia (NCD-22-11-004). Edimer Pharmaceuticals, Inc.

Ulm M R, Kratochwil A, Ulm B, Solar P, Aro G, Bernaschek, G. 1998. Three-dimensional ultrasound evaluation of fetal tooth germs. *Ultrasound Obst Gyn*. *12*(4): 240-3.

Zankl A, Addor M, Cousin P, Gaide A, Gudinchet F, Schorderet D. 2001. Fatal outcome in a female monozygotic twin with X-linked hypohidrotic ectodermal dysplasia (XLHED) due to a de novo t(X;9) translocation with probable disruption of the EDA gene. *Eur J Pediatr*. 160: 296-99.

Protocol Version 5
04 Dec 2014

Clinical Protocol

A Phase 2 open-label, dose-escalation study to evaluate the safety, pharmacokinetics, immunogenicity and pharmacodynamics/efficacy of EDI200, an EDA-A1 replacement protein, administered to male infants with X-Linked Hypohidrotic Ectodermal Dysplasia (XLHED)

Protocol: ECP-002

Investigational Product: EDI200

Sponsor:

Edimer Pharmaceuticals, Inc.
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IND Number: 109262
EudraCT Number: 2012-003561-17

Issue Date: 04DEC2014
Version: 5

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21NOV2014, version 5.1***
21NOV2014, version 5.2**
*Version 2 was issued prior to the enrollment of subjects and included only minor changes for clarification
**Version 3.1 was issued in UK only.
***Version 4 was issued in Germany only.

Amendment #/Date	Applicable Section	Original Text	New/Revised Text/Description	Rationale
5 21NOV2014	Executive Summary	Change made to add a third cohort.	In the case that EDI200 dosing at 10 mg/kg is well tolerated with no new safety issues identified during DSMB review, that cohort 2 EDI200 exposure levels are well below those at the neonate NOAEL level, and subject sweat production is not normalized at this dose, then cohort 3 subjects will be enrolled and dosed at a ½ log increase to 30 mg/kg/dose IV, equivalent to 0.15 x the neonate NOAEL of 200 mg/kg/dose (factor of 1:6.7). And other various minor changes to reflect a third cohort and increased dose.	Dose increase to 30 mg/kg
5 21NOV2014	Executive Summary	Male siblings of study subjects, both affected and unaffected, will be offered enrollment in an accompanying natural history sub-study including a medical history questionnaire and a one-time, non-invasive evaluation of current clinical condition (without study drug administration, X-rays or blood draws). The results from these genetically related, untreated siblings will	Male siblings of study subjects, both affected and unaffected, will be offered enrollment in an accompanying natural history sub-study including a medical history questionnaire and a one-time, non-invasive evaluation of current clinical condition (without study drug administration, skin biopsy samples, X-rays or blood draws). The results from these genetically related, untreated siblings will	Clarification

		provide comparative data for interpreting the clinical outcomes in treated study subjects.	provide comparative data for interpreting the clinical outcomes in treated study subjects.	
5 21NOV2014	Synopsis	N/A	Minor changes to reflect a third cohort and increased dose	Dose increase to 30 mg/kg
5 21NOV2014	Time and Events Schedule	N/A	Minor changes made to remove sweat duct density assessment and eye exam from the month 2 visit.	Data from the first four subjects does not support conducing these procedures at month 2.
5 21NOV2014	1.1	Change made to add a third cohort.	In the case that EDI200 dosing at 10 mg/kg is well tolerated with no new safety issues identified during DSMB review, that cohort 2 EDI200 exposure levels are well below those at the neonate NOAEL level, and subject sweat production is not normalized at this dose, then cohort 3 subjects will be enrolled and dosed at a ½ log increase to 30 mg/kg/dose IV, equivalent to 0.15 x the neonate NOAEL of 200 mg/kg/dose (factor of 1:6.7).	Dose increase to 30 mg/kg
5 21NOV2014		Cohort enrollment - The Phase 2 neonate XLHED study is designed to enroll two cohorts of at least 3 subjects each (cohort size determined by rate of enrollment and sponsor discretion), consistent with the practical aspects of study enrollment in ultra-rare orphan disorders and the unique challenge of enrolling newborns. Enrollment and dosing of all subjects in neonate cohort 1 (3 mg/kg/dose) will be completed and reviewed prior to initiating dosing of subjects in neonate cohort 2 (10 mg/kg/dose).	Cohort enrollment - The Phase 2 neonate XLHED study is designed to enroll up to three cohorts of at least 3 subjects each (cohort size determined by rate of enrollment and sponsor discretion), consistent with the practical aspects of study enrollment in ultra-rare orphan disorders and the unique challenge of enrolling newborns. Enrollment and dosing of all subjects in neonate cohort 1 (3 mg/kg/dose) will be completed and reviewed prior to initiating dosing of subjects in neonate cohort 2 (10 mg/kg/dose). Similarly, enrollment and dosing of	Dose increase to 30 mg/kg

			subjects in neonate cohort 2 will be completed and reviewed prior to enrollment and dosing of cohort 3 subjects (30 mg/kg/dose).	
5 21NOV2014	3.1.1	N/A	Various minor changes made regarding a third cohort.	Dose increase to 30 mg/kg
5 21NOV2014	3.1.2	Change made to add a third cohort.	Recognizing that translation from animal results and PK modeling to human study results may be imperfect, especially in the dose parameters, the protocol includes an option for enrolling a third cohort at a ½ log increase in dosing to 30 mg/kg/dose, again 5 doses over 15 days. It is anticipated that the criteria for initiating cohort 3 enrollment will include safety review of cohort 2 data by the DSMB including PK analysis, and a less than maximal clinical response in the cohort 2 subjects.	Dose increase to 30 mg/kg
5 21NOV2014	3.1.5	N/A	Various minor changes made regarding a third cohort.	Dose increase to 30 mg/kg
5 21NOV2014	3.3	6-10	9-15	Dose increase to 30 mg/kg
5 21NOV2014	3.3.8	N/A	Various minor changes made regarding a third cohort.	Dose increase to 30 mg/kg
5 21NOV2014	4.8	Change made to add a third cohort.	• After dosing is completed in XLHED cohort 2, the Sponsor may elect to enroll a third cohort with EDI200 dosing at 30 mg/kg/dose. Prior to initiating dosing of this third cohort, the DSMB will review safety and PK data from cohorts 1 and 2 in order to provide guidance on advancing to dosing at the higher level.	Dose increase to 30 mg/kg
5 21NOV2014	5.4	Changes made to remove sweat duct density	N/A	Data from the first four

		assessment and dry eye exam from the 2 month visit.		subjects does not support conducing these procedures at month 2.
5 21NOV2014	6.1	10 subjects	15 subjects	Dose increase to 30 mg/kg
5 21NOV2014	6.4	Changes made to remove sweat duct density assessment and dry eye exam from the 2 month visit.	N/A	Data from the first four subjects does not support conducing these procedures at month 2.
3 12JUN2013	Cover Page, Synopsis	A Phase 2 open-label, dose-escalation study to evaluate the safety, pharmacokinetics and pharmacodynamics/efficacy of EDI200, an EDA-A1 replacement protein, administered to male infants with X-Linked Hypohidrotic Ectodermal Dysplasia (XLHED)	A Phase 2 open-label, dose-escalation study to evaluate the safety, pharmacokinetics, immunogenicity and pharmacodynamics/efficacy of EDI200, an EDA-A1 replacement protein, administered to male infants with X-Linked Hypohidrotic Ectodermal Dysplasia (XLHED)	Immunogenicity added to study title
3 12JUN2013	Executive Summary	See 02APR2013 protocol version 2	Several minor changes made to Executive Summary	Clarification
3 12JUN2013	Time and Events Schedule	Change made to biopsy and PK sample schedule	Biopsy removed from Month 6 visit, PK sample removed from Day 15 visit	Correction and clarification
3 12JUN2013	Time and Events Schedule	Change made to PK sample schedule	PK sample added to baseline and month 6	Modification of PK sample schedule (similar minor changes made throughout protocol)
3 12JUN2013	Time and Events Schedule	Change made to safety labs and immunogenicity sample schedule	Safety labs and immunogenicity sample moved from day 15 to day 16	Modification of safety labs and immunogenicity sample schedule (similar minor changes made throughout protocol)
3 12JUN2013	Time and Events Schedule	A full physical exam will be conducted at baseline, treatment days 7 and 14 and at the months 2, 4 and	A full physical examination will be conducted at baseline, day 21, months 2, 4, and 6. With the full	Clarification on components of brief and full physical exam

		6 follow-up visits. The full physical exam will include weight, height, head circumference and vital signs. A brief physical exam will be conducted at treatment days 0, 1, 4, 11, 15 and 21. The brief physical exam will include vital signs. On dosing days vital signs will also be collected every 4 hours following the end of the infusion for 24 hours.	physical examination will be the following quantitative assessments; weight, height, head circumference and vital signs (temperature, blood pressure, heart rate and respiratory rate). A brief physical examination will be conducted at treatment days 0, 1, 4, 7, 11, 14 and 15. The brief physical examination will include overall appearance (normal or abnormal and if abnormal why), skin appearance, cardiovascular, pulmonary and abdominal evaluation. With the brief physical examination will be weight and a set of vital signs (temperature, blood pressure, heart rate and respiratory rate). On dosing days vital signs will also be collected pre- and post dosing as described in section 3.3.8.	
3 12JUN2013	Time and Events Schedule, 4.5.2	New text added	Time windows added for acceptable sampling	Provision for obtaining samples outside of specified time points
3 12JUN2013	Time and Events Schedule	Subjects may provide dental X-rays from an outside source. No dental radiographs will be obtained at the study site.	No dental radiographs will be taken as part of this sibling sub-study. Subjects will be asked to provide copies of recent dental X-rays from an outside source.	Clarification that no dental radiographs are done as part of the sibling sub-study (similar minor changes made throughout protocol)
3 12JUN2013	Time and Events Schedule	See 02APR2013, protocol version 2	Several minor changes made to Time and Events Schedule	Clarification
3 12JUN2013	1.1	See 02APR2013, protocol version 2	Several minor changes made	Clarification
3 12JUN2013	3	See 02APR2013, protocol version 2	Several minor changes made	Clarification
3 12JUN2013	3.1.5	The schedule of events for the In-Clinical portion of the study is presented in the	The subject will be admitted to the study site during the entire dosing period. The	Clarification of dosing stratification

		Time and Events Table. In each cohort the first subject enrolled will complete dosing of study medication, and if no significant AEs are observed then the remaining cohort subjects may begin dosing one week later. Subjects will have vital sign monitoring during and for 24 hours following each dose of study drug. The Medical Monitor and study PI will be responsible for evaluation of all AE and safety laboratory results.	schedule of events for this portion of the study is presented in the Time and Events Table. In each cohort, the first subject enrolled will complete the 15-day dosing period and undergo monitoring for an additional week at the study site. The site and Sponsor Medical Monitors will then review all AE and safety laboratory data. In the absence of any clinically significant AE's the remaining cohort subjects may begin dosing. It is anticipated that the timeframe from last dose of the first cohort subject through AE review will be approximately 2 weeks.	
3 12JUN2013	3.3.4, 3.3.6, 3.3.7	FDA	National Competent Authorities	Term FDA replaced with National Competent Authorities
3 12JUN2013	3.3.8	EDI200 will be thawed to room temperature on the day of dose administration, pooled in syringe(s) and infused via a syringe pump infusion system. The study drug shall be infused routinely over a period of 2 hours, but not to exceed 5 ml/kg/hr or 500 mg EDI200/hr.	EDI200 will be thawed to room temperature on the day of dosing, pooled in syringe(s) and administered via a syringe pump infusion system. The study drug shall be administered by slow IV infusion over at least 30 min, not to exceed 5 ml/kg/hour or 8.5 mg/min EDI200, in order to minimize the risk of infusion-related AE (refer to Investigational Brochure, Section 6.2). For more information on the preparation of EDI200 see the Pharmacy/Investigator Manual.	Clarification of infusion procedure
3 12JUN2013	3.3.8	New text added	During study drug administration and for 24 hrs following infusion the subject will have continuous heart rate and respiratory rate monitoring. A full set of vital signs including temperature, blood pressure, heart rate	Clarification of continuous monitoring (similar minor changes made throughout protocol)

			and respiratory rate will be documented on the following schedule: • Pre dosing - a single set of vital signs within 1 hour of initiating dose infusion • Post dosing: o 15 min after end of infusion, o 1 hr and 4 hrs after end of infusion, o then q4 hrs up to 24 hrs after end of infusion If the unit in which the subject is receiving study drug requires additional monitoring, then that data will be added to the subject's record.	
3 12JUN2013	3.3.8	New text added	The intravenous site will be assessed for patency and signs of local irritation prior to the start of the infusion, every 30 minutes during infusion, and at the end of study drug infusion.	Clarification of infusion site monitoring
3 12JUN2013	4.2.1	The initial physical examination will include assessment of standard developmental milestones, and will be augmented at Months 2, 4 and 6 by the Bayley Scales of Infant Development II (BSID-II), a well-validated assessment tool for use at 1-42 months of age (Black and Matula, 2000).	The initial physical examination will include assessment of standard developmental milestones, and will be augmented at Months 2, 4 and 6 by a validated, standard of care infant assessment tool. Examples of such tools include but are not limited to the Bayley Scales of Infant Development II (BSID-II) and III (BSDI-III) and the Denver Development Screening Test II (DDST II) (Black and Matula, 2000). Whichever tool is selected should be designed for ages down to 2 months of life and should be used for all follow-up visits.	Provision for the use of other tools of development assessment
3 12JUN2013	4.3	To meet inclusion criteria for study drug administration, families of	To meet inclusion criteria for EDI200 administration, potential study subjects are	Clarification of genetic testing done during

		potential study subjects will be asked if their male newborn has been tested for EDA mutations that confirm the XLHED diagnosis, either prenatally or postnatally. If genetic testing has been done, verbal consent from the family will be obtained to provide documentation of test results to the study site via a secure and confidential method including an option for electronic transmission. If not, the study site will provide a genotyping kit with an informed consent form directly to the family (no provision for fetal or amniotic fluid testing as part of this protocol). All genotyping costs will be covered by the study. It will be the responsibility of the family to have cord blood or a neonatal blood sample drawn and sent to the recommended genotyping laboratory.	required to have their XLHED diagnosis confirmed by genetic testing of the EDA gene and these test results relayed to the study site. EDA genetic testing itself is outside of the scope of this protocol. If requested, the families of prospective subjects in need of EDA genotyping will be referred to resources available to facilitate this testing. Consent from the family (written or verbal) will be obtained as part of the screening process to provide the study site with documentation of genetic testing results via a secure and confidential method including an option for electronic transmission.	screening
3 12JUN2013	4.5.1	New text added	It will be the Principal Investigator's responsibility to assess laboratory parameters against local reference ranges and to assess the clinical significance of any out of range values.	Clarification on assessment of lab values using both CTCAE criteria and local reference ranges
3 12JUN2013	4.6.2	The PI will report all SAEs to the Sponsor in a timely fashion, usually within 24 hours of awareness, by completing and faxing the SAE Report Form to CTI Safety as per directions described in the Study Reference Manual.	The PI will report all SAEs to the Sponsor in a timely fashion, within 24 hours of awareness, by completing and faxing the SAE Report Form to CTI Safety as per directions described in the Study Reference Manual.	Word "usually" deleted as reporting requirements are within 24 hours
3 12JUN2013	4.8	Unscheduled DSMB reviews will take place as outlined in Section 3.3.4-3.3.7 for single or accumulated	Unscheduled DSMB reviews will take place as outlined in Section 3.3.4-3.3.7 for single or accumulated adverse	Provision to allow for additional DSMB-

		adverse events.	events. Additional safety-related evaluations of one or more subjects may be requested by the DSMB based on findings through the 6 month, end-of-study visit.	requested procedures or visits
3 12JUN2013	5.5	New text added	The Sponsor or DSMB may request unscheduled visits either during the subject's participation in the Study or after his completion. The unscheduled visits may include additional safety-related evaluations (including blood sampling) based on findings through the 6-month, end-of-study visit.	Provision to allow for unscheduled visits

EXECUTIVE SUMMARY

X-linked hypohidrotic ectodermal dysplasia (XLHED) is a disorder of ectoderm development in which sweat and secretory gland hypoplasia predisposes affected infants to serious and potentially life-threatening hyperthermia and pneumonia (Clarke et al., 1987). Those XLHED patients who survive infancy face a host of ectoderm-related clinical conditions including failure to thrive, oligodontia and misshapen teeth, mid-face hypoplasia, eczema, chronic dry eyes, asthma, respiratory infections, sinusitis and chronic nosebleeds. XLHED is caused by inherited defects in the ectodysplasin gene (EDA, www.ncbi.nlm.nih.gov/omim) resulting in a deficiency of the ectoderm signaling protein EDA-A1. As is the general case with X-linked disorders, hemizygous XLHED males are more consistently and severely affected, while heterozygous XLHED females have a more variable phenotype.

In normal development, EDA-A1 acts as an ectoderm signaling molecule that binds specifically to the EDA-A1 receptor (EDAR) triggering initiation and maturation of ectoderm appendages into sweat and secretory glands, tooth buds and hair follicles. In the case of XLHED, EDA-A1 deficiency results in the absence or functional hypoplasia of the ectoderm appendages. There are no therapies currently available for XLHED that prevent or correct the underlying ectodermal abnormalities.

EDI200 is a fully humanized EDA-A1 replacement molecule under development as a novel therapeutic for XLHED. EDI200 comprises the human IgG1 Fc domain linked to the human EDA-A1 receptor-binding domain. In the course of normal ectodermal signaling, EDA-A1 monomers associate as trimers and higher order multimers that are required for activation of the EDA-A1 receptor (EDAR). The N-terminal Fc receptor portion of the EDI200 molecule serves to stabilize the intermolecular EDA-A1 associations required for EDAR binding, and to provide a potential mechanism for transplacental delivery (Miller, 2003).

On-target EDI200 activation of the EDA-A1/EDAR signaling pathway *in vivo* is evidenced by the remarkable phenotypic response in preclinical models. In XLHED-affected animals, EDI200 correction of EDA-A1 deficiency prenatally (mice) or postnatally (newborn mice and dogs) resulted in a significant and sustained improvement in the health of the treated animals (Gaide and Schneider, 2003; Casal et al., 2007; Mauldin et al., 2009). Postnatal studies in both mice and dogs demonstrated a consistent and restricted window of efficacy (Gaide and Schneider, 2003; Edimer Study NCD-11-200-005). These results support the clinical development of EDI200 as a therapeutic to be administered to XLHED-affected patients in the neonatal period or earlier.

This Phase 2 first-in-neonate study will enroll treatment-naïve, XLHED-affected male newborns for EDI200 administration initiated within the first two weeks of life. All subjects will meet entry criteria including documentation of an EDA mutation associated

with XLHED. Following Baseline evaluations, EDI200 dosing will be initiated between day-of-life (DOL) 2 and 14, with each study subject receiving 2 doses/week for a total of 5 doses. This dosing regimen mirrors that used to enhance efficacy in the dog XLHED model, considered to be most relevant to the clinical study design. Comprehensive safety, pharmacokinetic (PK), immunogenicity and pharmacodynamic (PD)/efficacy evaluations of all neonate study subjects will initiate at study enrollment and continue throughout the dosing and follow-up period (to age 6 months).

The study will enroll 9-15 subjects in up to three cohorts, with a minimum of 3 subjects per cohort. Given the challenge of identifying families where the potential study subject is yet to be born, it is expected that cohort size and time for recruitment will be variable. We anticipate enrolling subjects over a 12-24 month period. Cohort 1 study subjects will each be administered EDI200 IV at 3 mg/kg/dose x 5 doses, equivalent to 0.015 x the neonate no observed adverse effect level (NOAEL) of 200 mg/kg/dose (factor of 1:66) and well below the maximum safe starting dose in initial clinical trials as suggested by FDA guidance. This dose was associated with partial efficacy in the canine XLHED model considered most relevant to the clinical study, and was well tolerated by XLHED adults in the Phase 1 safety study (NCT01564225, www.clinicaltrials.gov)

All safety laboratory studies will be done at the individual study sites and available to the Data Safety Monitoring Board (DSMB) in real time. Following dosing of all subjects in neonate cohort 1, the DSMB will review the cohort 1 safety and PK data. If no new safety issues are identified then cohort 2 subjects will be enrolled and dosed at a ½ log increase to 10 mg/kg/dose IV, equivalent to 0.05 x the neonate NOAEL of 200 mg/kg/dose (factor of 1:20). This dose was associated with enhanced efficacy in the canine XLHED model. Prior to the dosing of XLHED neonates in cohort 2, the DSMB also will have reviewed the safety and PK data from XLHED adult cohort 2 subjects dosed at the same 10 mg/kg/dose and the same 5 dose regimen.

In the case that EDI200 dosing at 10 mg/kg is well tolerated with no new safety issues identified during DSMB review, that cohort 2 EDI200 exposure levels are well below those at the neonate NOAEL level, and subject sweat production is not normalized at this dose, then cohort 3 subjects will be enrolled and dosed at a ½ log increase to 30 mg/kg/dose IV, equivalent to 0.15 x the neonate NOAEL of 200 mg/kg/dose (factor of 1:6.7).

In the core study, primary outcome measures will be safety, PK and immunogenicity. Secondary outcome evaluations of pharmacodynamics (PD)/efficacy will incorporate growth and development parameters, frequency of infections and hospitalizations, facial development as monitored by computerized recognition of XLHED-associated features, and assessments of ectoderm-related physiologic functions using technologies that minimize risk to this population. From 6 months onward (end of data collection in

the Phase 2 core study), the EDI200-exposed infants will be enrolled in a long-term extension study with yearly safety and age-appropriate PD/efficacy evaluations.

Male siblings of study subjects, both affected and unaffected, will be offered enrollment in an accompanying natural history sub-study including a medical history questionnaire and a one-time, non-invasive evaluation of current clinical condition (without study drug administration, skin biopsy samples, X-rays or blood draws). The results from these genetically related, untreated siblings will provide comparative data for interpreting the clinical outcomes in treated study subjects.

SYNOPSIS

Title of Study	A Phase 2 open-label, dose-escalation study to evaluate the safety, pharmacokinetics, immunogenicity and pharmacodynamics/efficacy of EDI200, an EDA-A1 replacement protein, administered to male infants with X-Linked Hypohidrotic Ectodermal Dysplasia (XLHED)
Name of Company	Edimer Pharmaceuticals, Inc.
Name of Finished Product	EDI200
Name of Active Ingredient	EDI200
Protocol Number	ECP-002
IND Number	109262
EudraCT Number	2012-003561-17
Objectives	Primary Objectives • To assess the safety, pharmacokinetics and immunogenicity of EDI200 administered to XLHED-affected neonates Secondary Pharmacodynamic/Efficacy Objectives • To assess EDI200 pharmacodynamics/ efficacy in the treatment of XLHED-affected neonates • To compare clinical and medical history data obtained from untreated male siblings to that of the XLHED-affected neonate receiving study drug
Methodology	Phase 2 open-label, three cohort, dose-escalation study
Number of Subjects	• 9-15 XLHED-affected male neonates for study drug administration • Male siblings (XLHED-affected and unaffected) as historical controls
Diagnosis and Main Criteria for Inclusion	Male neonates documented by genetic diagnosis to carry an EDA mutation associated with XLHED, and their male siblings
Test Product Dose, Route of Administration	3, 10 or 30 mg/kg/dose (IV)
Duration of Treatment	5 doses over 15 days

Pharmacodynamic/Efficacy Evaluations	• Growth and development • Infections and hospitalizations • Dentition • Facial development • Sweat gland number and function • Dry eye assessment • Thermoregulation • Skin biopsy for expression profile
Safety Evaluations	Safety laboratory blood tests, Vital Signs, Adverse Events
Pharmacokinetics Evaluations	Serial blood draws
Statistical Methods	The safety population will consist of all subjects who receive at least one dose of study medication. The PK population will consist of all subjects who receive at least one dose of study medication and have sufficient data points to obtain a plasma concentration by time profile. The PD/efficacy population will consist of all subjects who receive at least one dose of study medication and complete the follow-up assessments through at least month 2.

TIME AND EVENTS SCHEDULE – MULTI-DOSE EDI200 ADMINISTRATION

	Screening		Baseline	Treatment Phase										Follow-up Visits	Study Completion
	Prenatal[1] (Optional)	Postnatal[2] DOL 2 to DOL 12	DOL 2 to DOL 14[3]	TD 0	TD 1	TD 2	TD 4	TD 7	TD 11	TD 14	TD 15	TD 16	TD 21	Mon 2 & 4 of Life[4] (± 1 wk)	Mon 6 of Life[4] (± 2 wks)
Informed Consent	X	X	X												
Inclusion/Exclusion	X	X	X												
Genetic testing			X[5]												
Medical History	X	X[6]	X												
Safety Evaluations															
Physical Examination[7]			X	X	X		X	X	X	X	X		X	X	X
Safety Laboratory			X		X							X	X	X[8]	X
Immunogenicity			X									X		X[8]	X
Pharmacokinetic[9]			X	X	X	X				X		X	X	X[8]	X
PD/Efficacy															
Growth/Development			X											X	X
Dentition[10]			X												
Facial Development[11]			X												X
Sweat Assessments			X											X[8]	X
Dry eye Assessment			X												X
Thermoregulation[12]			X										X		
Skin biopsy sample			X		X						X				
Study Drug				X			X	X	X	X					
Adverse Events/Con Meds[13]	X														

TIME AND EVENTS SCHEDULE – MALE SIBLINGS OF STUDY SUBJECTS

	Study Enrollment	Evaluation
	From date of 1st dose study drug administered to affected sibling	Prior to Study Completion for affected sibling
Informed Consent	X	
Inclusion/Exclusion Criteria	X	
Medical History	X	
Safety Evaluations		
Physical Examination		X
Weight, Height, Vital Signs		X
XLHED-associated Outcomes		
Growth/Development		X
Infections/Hospitalizations		X
Dentition		X[14]
Facial Development		X[15]
Sweat Assessments		X
Pulmonary function[16]		X
eNO level[17]		X
Dry eye Assessment[18]		X
Adverse Events & Con Meds	X	

1. Optional prenatal screening enrollment is from end of first trimester through delivery date
2. Newborn's screening window for study inclusion is through DOL #12
3. Baseline evaluations must be completed by DOL #14
4. Follow-up visits at 2, 4 and 6 months of chronologic age
5. In the Screening process, confirmation of subject EDA genotype is required from the family. Under Baseline Events, EDAR genotyping for the phenotype-modifying polymorphism EDAR V370A will be a standard assessment (Cluzeau et al., 2012) but is not required prior to study drug administration
6. Medical history encompasses antenatal and perinatal findings including antenatal ultrasound imaging of tooth buds if performed (Ulm et al., 1998)
7. A full physical examination will be conducted at baseline, day 21, months 2, 4, and 6. With the full physical examination will be the following quantitative assessments: weight, height, head circumference and vital signs (temperature, blood pressure, heart rate and respiratory rate). A brief physical examination will be conducted at treatment days 0, 1, 4, 7, 11, 14 and 15. The brief physical examination will include overall appearance (normal or abnormal and if abnormal why), skin appearance, cardiovascular, pulmonary and abdominal evaluation. With the brief physical examination will be weight and a set of vital signs (temperature, blood pressure, heart rate and respiratory rate). On dosing days vital signs will also be collected pre- and post dosing as described in section 3.3.8.
8. Studies to be performed at 2 months but not at the 4-month visit. The 2-month evaluation will include pilocarpine-induced sweating but not confocal imaging (sweat duct density).
9. PK samples drawn pre-EDI200 dosing and post-end of infusion at approximately the following time points:

	Pre-Dose	Post-Dose							
		15 (±5) min	3 (±.5) hrs	8 (±1) hrs	18 (±2) hrs	24(±2) hrs	48 (±4) hrs	168(±8) hrs	Age 2 months (±1 wk) & 6 months (±2 wks)
D0 (dose 1)	X	X	X	X		X	X		
D14 (dose 5)	X	X	X		X		X	X	X

10. Baseline lateral jaw film only. Dental evaluation to be performed in the long-term extension study will minimize the use of dental radiographs, and allow for substitution of dental imaging obtained as part of the routine care of XLHED patients.

11. Digital analysis of non-invasive 2D facial photographs is a technology under development jointly by the Sponsor and a private company and is being explored as a tool for monitoring change in craniofacial appearance. The algorithm assesses the subject's facial structures in the neonatal period and continues through photographs taken in the extension study.
12. Thermoregulation assessment in the neonatal period is a well-documented procedure monitoring short-term temperature and vital sign response in a closed system (incubator). At an older age in the extension study, exercise-related thermoregulation will be assessed.
13. Infections/hospitalizations as PD/efficacy endpoint will be captured through adverse events
14. No dental radiographs will be taken as part of this sibling sub-study. Subjects will be asked to provide copies of recent dental X-rays from an outside source.
15. Frontal and lateral facial photographs to be taken and baby picture (age up to 1 month) to be collected if available
16. Minimum age 5 years for pulmonary testing
17. Minimum age 4 years for eNO assessment
18. A more comprehensive dry eye assessment will be performed in children as opposed to the neonates

LIST OF ABBREVIATIONS

Abbreviation	Definition
2D	Two Dimensional
ADL	Activities of Daily Living
AE	Adverse Event
AUC	Area Under the Curve
BSID	Bayley Scales of Infant Development
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTGF	Connective Tissue Growth Factor
DDST	Denver Development Screening Test
DOL	Day of Life
DSMB	Data Safety Monitoring Board
EDA	Ectodysplasin A
EDA-A1	Ectodysplasin protein A1
EDAR	Ectodysplasin-A1 Receptor
EDC	Electronic Data Capture
eCRF	Electronic Case Report Forms
eNO	Exhaled Nitric Oxide
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
I/E	Inclusion/Exclusion
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
Lgr5	Leucine-Rich G-Protein Coupled Receptor
MedDRA	Medical Dictionary for Regulatory Activities
NCD	Nonclinical Document
NCI	National Cancer Institute
NOAEL	No Adverse Effect Level
OSDI	Ocular Surface Disease Index
PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetic
RNA	Ribonucleic Acid
SAE	Serious adverse event

Shh	Sonic Hedgehog
SUSAR	Suspected Unexpected Adverse Reaction
TD	Treatment Day
XLHED	X-Linked Hypohidrotic Ectodermal Dysplasia

PI AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

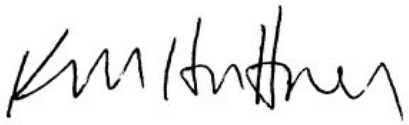
I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the conduct of the study.

PI's Signature* Date

Name of PI (Typed or Printed)

Institution Address*

Phone Number*



04DEC2014

Sponsor's Medical Monitor Signature Date

Kenneth Huttner, MD, PhD

Name of Medical Monitor (Typed or Printed)

* If the address or phone number of the PI changes during the course of the study, written notification will be provided by the PI to the Sponsor and will not require protocol amendment(s).

1 BACKGROUND

XLHED, the most common of the ectodermal dysplasias, is caused by inherited defects in the ectodysplasin (EDA) gene that disrupt synthesis and/or function of the primary translational product EDA-A1 (www.ncbi.nlm.nih.gov/omim). In normal development, EDA-A1 acts as an ectoderm signaling molecule that binds specifically to the EDA-A1 receptor (EDAR) triggering initiation and maturation of ectoderm appendages into sweat and secretory glands, tooth buds and hair follicles. The absence of normal EDA-A1 expression results in sweat and secretory gland hypoplasia predisposing XLHED-affected infants to serious and potentially life-threatening hyperthermia and pneumonia (Clarke et al., 1987). XLHED-affected children surviving infancy face a host of life-long ectoderm-related clinical conditions including failure to thrive, oligodontia and misshapen teeth, mid-face hypoplasia, eczema, chronic dry eyes, asthma, respiratory infections, sinusitis and chronic nosebleeds. As is the general case with X-linked disorders, XLHED-affected males are more consistently and severely affected, while XLHED-affected females have a more variable phenotype.

There are no therapies currently available for XLHED that prevent or correct the underlying abnormalities of ectoderm-derived structures. In two genetically confirmed animal models of XLHED, systemic administration of recombinant EDA-A1 (EDI200) in the prenatal (mice) or postnatal (newborn mice and dogs) settings corrected many of the defects in ectoderm development resulting in a significant and sustained improvement in the health of the treated animals (Gaide and Schneider, 2003; Casal et al., 2007). To date, data in both species has demonstrated a restricted efficacy window that closes after the first several weeks of postnatal life (Gaide and Schneider, 2003; Edimer Study NCD-200-11-005). This is consistent with the well-studied timeframe for ectoderm appendage development, and supports the clinical development of EDI200 as a therapeutic to be administered to XLHED-affected patients in the newborn period or earlier.

1.1 Rationale for Study

Study Drug - EDI200 is a fully humanized EDA-A1 replacement molecule designed for parenteral administration, comprising the human IgG1 Fc sequence linked to the human EDA-A1 receptor-binding domain. The N-terminal Fc receptor portion of the EDI200 molecule serves to facilitate and stabilize the intermolecular associations required for EDAR binding, as well as providing a potential mechanism for fetal delivery (Miller, 2003). Through its unique design, EDI200 retains the EDA-A1 receptor specificity as evidenced by the targeted phenotype response in preclinical XLHED models (Gaide and Schneider, 2003; Casal et al., 2007; Mauldin et al., 2009).

Safety and PK data in Adults - Following discussions with the FDA regarding the clinical development plan for EDI200 in a pediatric indication; a Phase 1 study in XLHED-affected adults was initiated (NCT01564225, www.clinicaltrials.gov) to develop human safety and PK data in anticipation of dosing XLHED-affected neonates. Selecting XLHED-affected adults for

the Phase 1 study provided a genetic and biologic relevance to XLHED-affected neonates. Enrolling adult XLHED-affected males and females: (1) supported dosing of male XLHED neonates in the current trial; (2) provided data for the possibility of dosing XLHED-affected female neonates; and (3) initiated the collection of data necessary to support a future trial of maternal EDI200 administration. Identical dosage (mg/kg) and dosing regimens are planned for the adult and neonate XLHED studies.

Neonate Dosing Strategy: Age at Dosing Initiation; Dosing Regimen; Starting Dose

Age at Dosing Initiation – In both the mouse and dog XLHED models; early postnatal administration was associated with correction of clinically relevant abnormalities. Based primarily on the multi-dose dog data, study drug administration in this protocol is targeted to begin between day-of-life (DOL) #2 and DOL #14 (Edimer Study NCD-200-11-005).

Dose Regimen - The EDI200 dosing regimen proposed for the Phase 2 XLHED neonate study is a single course consisting of 5 doses administered at 2 doses/week. This regimen is based on results from the dog XLHED model which is most comparable to the human condition in developmental maturity at birth and in health-related endpoints (Casal et al., 2007; Edimer Study NCD-200-11-004). The 2-dose/week-regimen was incorporated into the GLP toxicology studies as well (Edimer Studies 1800-009 and 1800-010).

Starting Dose – No study-drug related adverse effects were observed at the highest EDI200 dose tested in both mouse and dog neonatal GLP toxicology studies, confirming a NOAEL of ≥200 mg/kg/dose (1800-009; 1800-010). Consistent with FDA guidelines for Maximum Starting Dose in Initial Clinical Trials, and incorporating a conservative approach to dosing in this vulnerable population, the first cohort of XLHED neonates will receive EDI200 at 3 mg/kg/dose IV, 0.015 x neonatal NOAEL (factor of 1/66). In the dog XLHED efficacy studies, dosing at 3 mg/kg/dose was associated with partial efficacy, which was enhanced significantly in animals receiving 10 mg/kg/dose (Edimer Study NCD-200-11-004). Safety and PK data from the Phase 1 adult study cohort treated with EDI200 at 3 mg/kg/dose x 5 doses over 15 days was reviewed by the DSMB with no reported study drug-related adverse events.

In the Phase 2 neonate study, the DSMB will review safety and PK data from neonate cohort 1, and in the absence of safety concerns, neonates will then be enrolled in cohort 2 and dosed at a pharmacologic half-log increase to EDI200 10 mg/kg/dose IV, equivalent to 0.05 x the neonatal NOAEL (factor of 1/20). Safety and PK data from the Phase 1 adult cohort 2, having received EDI200 at the same dose and the same dosing regimen, also will be reviewed by the DSMB prior to initiating dosing in neonate cohort 2. The dose for XLHED neonate cohort 2 is anticipated to maximize postnatal EDI200 efficacy based on the dog XLHED results (Edimer Study NCD-200-11-004).

In the case that EDI200 dosing at 10 mg/kg is well tolerated with no new safety issues identified during DSMB review, that cohort 2 EDI200 exposure levels are well below those at

the neonate NOAEL level, and subject sweat production is not normalized at this dose, then cohort 3 subjects will be enrolled and dosed at a ½ log increase to 30 mg/kg/dose IV, equivalent to 0.15 x the neonate NOAEL of 200 mg/kg/dose (factor of 1:6.7).

Cohort enrollment - The Phase 2 neonate XLHED study is designed to enroll up to three cohorts of at least 3 subjects each (cohort size determined by rate of enrollment and sponsor discretion), consistent with the practical aspects of study enrollment in ultra-rare orphan disorders and the unique challenge of enrolling newborns. Enrollment and dosing of all subjects in neonate cohort 1 (3 mg/kg/dose) will be completed and reviewed prior to initiating dosing of subjects in neonate cohort 2 (10 mg/kg/dose). Similarly, enrollment and dosing of subjects in neonate cohort 2 will be completed and reviewed prior to enrollment and dosing of cohort 3 subjects (30 mg/kg/dose).

Primary objectives - Safety labs, physical examination, vital signs, adverse events and concomitant medications, immunogenicity, and PK will be documented as outlined in the Time and Events schedule. The schedule for PK sampling, based on the preclinical and Phase 1 adult XLHED dosing results, incorporates a sparse sampling approach to limit the frequency and volumes of neonatal blood draws. The proposed PK sampling maximizes data collection for determining both the AUC and Cmax.

Pharmacodynamic/efficacy objectives - PD/efficacy endpoint assessments relevant to the biology and pathophysiology of XLHED are incorporated into the study design as outlined in the Time and Events:

- *Clinical endpoints* - growth and development (including feeding history), infections and hospitalizations (captured under adverse events).
- *Imaging assessments* - diagnostic dental radiographs (the post-treatment dental X-rays will be incorporated into the long-term extension study and hence are not described further in this protocol), antenatal ultrasound results for tooth bud development (if available as part of Obstetric care, documented in the Medical History), pre- and post-treatment facial photographs to assess changes in craniofacial features associated with XLHED and its correction.
- *Clinical biomarkers* - sweat duct number and induced sweat volume, thermoregulation and dry eye evaluation.
- *Molecular biomarkers* - skin biopsy for expression profile.

All affected and unaffected male siblings of study subjects will be offered enrollment in a natural history sub-study evaluating the medical history and clinical condition of genetically related, untreated comparators for the study subjects.

Study Duration - Total study duration for each subject receiving study drug will be approximately 6 months, including a treatment and safety/efficacy monitoring period. A long-

term extension study for all subjects receiving study drug will continue safety and PD/efficacy evaluations. Study duration for male siblings in the sibling sub study will be 1-2 days.

2 OBJECTIVES

2.1 Primary Objectives

To assess the safety, pharmacokinetics and immunogenicity of EDI200 administered to XLHED-affected neonates

2.2 Pharmacodynamic/Efficacy Objectives

- To assess the pharmacodynamics/efficacy of EDI200 administered to XLHED-affected neonates
- To compare clinical data and medical history obtained from untreated male siblings to that of the XLHED-affected neonates receiving study drug

3 STUDY DESIGN

3.1 Multi-Dose EDI200 Administration

3.1.1 *Brief Description and Rationale for Study Design*

X-linked hypohidrotic ectodermal dysplasia (XLHED) is a disorder of ectoderm development associated with EDA gene mutations that lead to a deficiency of the ectoderm signaling protein EDA-A1. EDI200 is a fully humanized EDA-A1 replacement molecule under development as a novel therapeutic for XLHED. In two XLHED animal models, a single course of perinatal EDI200 administration resulted in a substantial correction of abnormalities in ectoderm development and a significant improvement in the health of the treated animals (Gaide and Schneider, 2003; Casal et al., 2007). These preclinical findings support the clinical development of EDI200 as a therapeutic to be administered to XLHED-affected patients in the neonatal period or earlier.

The open-label Phase 2 study of EDI200 administered to XLHED-affected neonates will enroll 9-15 subjects in up to three sequential cohorts. Each study subject will have documentation of an EDA gene mutation. Cohorts will be enrolled sequentially, i.e. the first subjects will all be enrolled in cohort 1, and only after cohort 1 safety evaluation by the DSMB will subjects be enrolled in cohort 2 for dosing at a higher level. The same level of review will be applied in advancing the dosing from cohort 2 to cohort 3 subjects. Final cohort size will be determined by subject and site availability, with at least 3 subjects per cohort.

The EDI200 dose for subjects in cohort 1 is 3 mg/kg/dose, consistent with the FDA Guidelines for Maximum Safe Starting Dose in Initial Clinical Trials based on the neonate NOAEL of $\geq$200 mg/kg/dose. This dose is anticipated to be associated with partial efficacy based on the dog XLHED studies. Safety laboratory results will be available to the DSMB in real time, and a formal DSMB safety and PK review will occur following completion of dosing in cohort 1. Additionally, the DSMB will have available to it safety and PK data from all XLHED-affected adult subjects from the Phase 1 adult safety study (NCT01564225, www.clinicaltrials.gov). In the absence of a safety signal or PK concern from DSMB review, XLHED neonates in cohort 2 will be dosed at 10 mg/kg/dose, a half-log pharmacologic increase to a dose anticipated to maximize clinical benefit based on the XLHED dog studies. Cohort 3 enrollment will follow DSMB review of data from cohorts 1 and 2, including an analysis of PK parameters.

Primary outcome measures for all subjects will be safety, PK and immunogenicity. Study duration is 6 months with all subjects rolling over into a long-term extension study providing yearly evaluations. Pharmacodynamic/efficacy objectives in the Phase 2 neonate study will be limited by the timeline for ectodermal development that often exceeds 6 months, e.g. dentition. Therefore, several of these endpoints will be incorporated into the extension study protocol. There will be assessment of the following: (1) endpoints relevant to the common clinical findings in XLHED using age-appropriate technologies, e.g. growth and development,

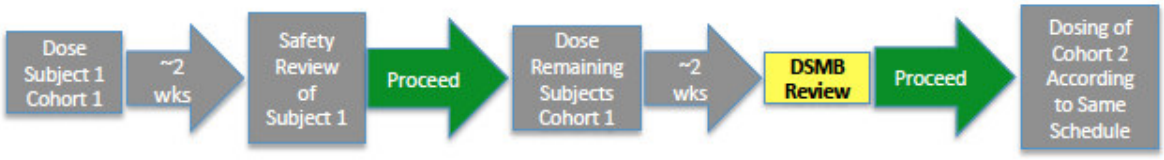
infections and hospitalizations, sweat duct counts and stimulated sweat production, pre-treatment dentition, and thermoregulation; (2) change from baseline in craniofacial structures using a non-invasive facial recognition software program based on subject digital facial photographs (Appendix 1); and (3) change in molecular expression profile using skin biopsy samples obtained pre- and post-study drug exposure.

3.1.2 *Starting and Target Dose/Dosing Regimen*

The proposed starting dose is consistent with the FDA Guidelines for Maximum Safe Starting Dose in Initial Clinical Trials, based on the neonate GLP toxicology studies in two species that demonstrated a NOAEL of ≥200 mg/kg (MPI Study 1800-009 and 1800-010). Cohort 1 subjects will be dosed with EDI200 at 3 mg/kg/dose IV, 0.015 x neonate NOAEL (factor of 1/66). The proposed dosing regimen of 2 doses/week x 5 doses, beginning within the first 2 weeks of life, is supported by the dosing regimen in the GLP toxicology studies. This dose and dosing regimen is in the range of anticipated partial efficacy in the dog XLHED model, considered the most relevant species for endpoint assessment.

Prior to enrolling subjects in neonate cohort 1, the DSMB reviewed safety and PK data from cohort 1 in the Phase 1 XLHED study (NCT01564225) where adult XLHED subjects were administered EDI200 at the same dose (3 mg/kg/dose) and dosing regimen (5 doses total at 2 doses/week). No study drug-related adverse events were reported. In neonate cohort 1, the first subject enrolled will complete dosing followed by a ~2-week safety review. If no safety concerns are observed, the remaining cohort 1 subjects will begin dosing. Dosing for individual subjects will be on a mg/kg basis.

Once all subjects in neonate cohort 1 have received their IV dosing, the DSMB will review safety and PK data. In the absence of safety concerns following DSMB review of cohort 1 data, neonates in cohort 2 will be dosed at a pharmacologic half-log increase to 10 mg/kg/dose, 0.05 x neonate NOAEL (factor of 1/20), following the same 5-dose regimen (see figure below). The dose and dosing regimen for neonate cohort 2 is in the range anticipated to maximize postnatal efficacy based on results from the dog XLHED model. Dosing of subjects in cohort 2 is sequential as described in cohort 1. Subject enrollment and cohort initiation will be according to the following schedule:

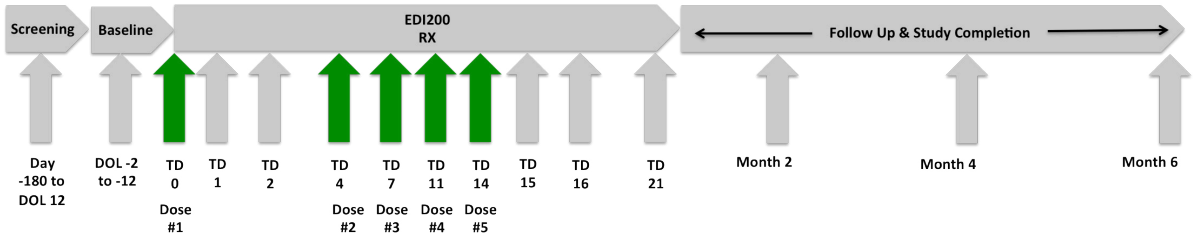


*The above schedule is repeated in cohort 2 to proceed to cohort 3

Recognizing that translation from animal results and PK modeling to human study results may be imperfect, especially in the dose parameters, the protocol includes an option for enrolling a

third cohort at a ½ log increase in dosing to 30 mg/kg/dose, again 5 doses over 15 days. It is anticipated that the criteria for initiating cohort 3 enrollment will include safety review of cohort 2 data by the DSMB including PK analysis, and a less than maximal clinical response in the cohort 2 subjects. The study will be conducted in age-appropriate clinical facilities by medical staff with appropriate levels of training and expertise and an understanding of the investigational medicinal product, its target and mechanism of action. There will be immediate access to facilities for the treatment of medical emergencies including an Intensive Care Unit.

The study timeline and visit dates for each subject are as follows:



3.1.3 *Screening*

A family with a male fetus/newborn with a clinical suspicion of XLHED may inquire to receive study information by phone, email or directly at a study site (also available on www.clinicaltrials.gov). If the family then wishes to be considered for study participation, they have the following options:

1. Prenatal Screening Enrollment (optional): the family of a male fetus at risk for XLHED may provide Informed Consent (ICF1) for data collection to begin in order to evaluate eligibility for newborn EDI200 treatment (see Sections 3.3.1 and 3.3.2). Entering the screening process early will allow for discussion and planning to minimize the potential family disruption that is likely to accompany early postnatal transfer to the study site if the subject is to be enrolled in the treatment protocol. The language of ICF1 will state clearly that once all Inclusion/Exclusion (I/E) criteria are met, an additional Informed Consent (ICF2), obtained postnatally, will be required in order to enroll the XLHED-affected neonate into the treatment portion of the study. The enrollment window for treatment encompasses the period from DOL #2 through DOL #12 (allowing a minimum of two days for transfer to the study site and baseline assessments prior to DOL #14, the last day study drug dosing can be initiated).

2. Postnatal Screening Enrollment: in the absence of Prenatal Screening Enrollment, the family of a male newborn at risk for XLHED may provide Informed Consent (ICF1) for data collection to begin in order to evaluate eligibility for the newborn EDI200 treatment (see Sections 3.3.1 and 3.3.2). The language of ICF1 will state clearly that once all Inclusion/Exclusion (I/E) criteria are met, an additional Informed Consent (ICF2) will be required in order to enroll the XLHED-affected neonate into the treatment portion of the study. The enrollment window for

treatment encompasses the period from DOL #2 through DOL #12 (allowing a minimum of two days for transfer to the study site and baseline assessments prior to DOL #14, the last day study drug dosing can be initiated).

A key inclusion criterion for the treatment protocol is verification of the XLHED diagnosis through EDA mutation testing. As part of the screening process, genetic testing results may be provided by the family to the study site via a secure and confidential method including the option for electronic transmission. If genotyping confirmation is not available at the time of Screening Informed Consent, the families of prospective subjects will be referred to resources available to facilitate rapid genotype testing at an accredited laboratory.

Families may be considering delivery at a clinical study site to facilitate treatment of their XLHED-affected son as soon as possible after birth. Any such decision is outside of this protocol and would be a private matter between the family, their health care providers, their insurance company, and the delivery service at the study site. Delivery at the study site would not commit the family to have their newborn participate in the treatment protocol, nor would it commit the PI and study site to enroll the XLHED-affected male neonate unless and until he met all the required I/E criteria and a treatment Informed Consent (ICF2) was signed by both parents (if reasonably available).

If the XLHED-affected neonate meeting inclusion/exclusion criteria is not born at the study site, the study team will assist in and cover all reasonable expenses associated with his transfer to the site. If medical transport is required, this will occur under specific Informed Consent (ICF-T) requiring signatures of both parents (if reasonably available). The window for transfer to the study site must allow for the neonate to complete Baseline evaluations in a timely manner prior to DOL #14.

3.1.4 *Baseline*

Baseline evaluation will begin with confirmation of treatment inclusion/exclusion criteria and documentation of relevant family, pregnancy and neonatal medical history. Baseline assessments of the XLHED-affected male infant as described below are to be completed prior to first dose study drug. To date, there is little data published describing evaluation techniques for XLHED patient in the newborn period. The Sponsor has experience with using the novel, minimally invasive technologies that are incorporated into this study protocol (www.edimerpharma.com/Publications and News/Publications and Abstracts)

In this Phase 2 protocol, baseline assessments of the neonate study subjects will serve three purposes. First, they will verify the general health of the XLHED-affected infant including documentation of developmental status and full physical examination. Second, blood samples will be collected for pre-treatment safety laboratory values, documentation of the absence of EDI200 and anti-EDI200 antibodies, and genotyping of the EDAR V370A polymorphism that has the potential to modify the XLHED-phenotype. Third, they will document pre-treatment

ectoderm status related to EDA-A1 deficiency, including sweat duct number, induced sweat volume, presence/absence of dentition on lateral jaw radiograph, dry eyes, digital 2D facial photograph for XLHED facial appearance, thermoregulation imbalance and skin biopsy for expression profile.

3.1.5 *Treatment Period*

The subject will be admitted to the study site during the entire dosing period. The schedule of events for this portion of the study is presented in the Time and Events Table. In each cohort, the first subject enrolled will complete the 15-day dosing period and undergo monitoring for an additional week at the study site. The site and Sponsor Medical Monitors will then review all AE and safety laboratory data. In the absence of any clinically significant AE's the remaining cohort subjects may begin dosing. It is anticipated that the timeframe from last dose of the first cohort subject through AE review will be approximately 2 weeks.

Each subject will be administered 5 doses of EDI200, administered IV on Treatment Days (TD) 0, 4, 7, 11 and 14, with vital sign monitoring during and for 24 hours following each dose of study drug. The Treatment Day for doses two through five may be $\pm$1 day, but doses must be at least 48 hours apart. Subjects in cohort 1 will be dosed at 3 mg/kg/dose calculated on Baseline weight.

On TD 0, subjects will have the following evaluations performed prior to dosing: brief physical exam, AE and concomitant medication assessment. Subjects will be administered dose 1 of study drug with vital sign monitoring during and for 24 hrs post-dose. Full details of the vital sign monitoring plan are described in Section 3.3.8. Sparse PK sampling time points post-dosing are described in Section 4.5.2.

On TD 1, subjects will have the following evaluations performed: brief physical exam, AE and concomitant medication assessment, safety laboratories, PK sampling and skin biopsy for expression profile (both approximately 24-hour post dose 1).

On TD 2, subjects will have the following evaluations performed: AE and concomitant medication assessment and PK sampling (approximately 48-hour post dose 1).

On TD 4, subjects will have the following evaluations performed prior to dosing: brief physical exam, AE and concomitant medication assessment. Subjects will be administered dose 2 of study drug with vital sign monitoring during and for 24 hrs post-dose.

On TD 7, subjects will have the following evaluations performed prior to dosing: brief physical exam and AE and concomitant medication assessment. Subjects will be administered dose 3 of study drug with vital sign monitoring during and for 24 hrs post-dose.

On TD 11, subjects will have the following evaluations performed prior to dosing: brief physical exam and AE and concomitant medication assessment. Subjects will be administered dose 4 of study drug with vital sign monitoring during and for 24 hrs post-dose.

On TD 14, subjects will have the following evaluations performed prior to dosing: brief physical exam and AE and concomitant medication assessment, and PK sampling. Subjects will be administered dose 5 of study drug with vital sign monitoring during and for 24 hrs post-dose. Sparse PK sampling time points post-dosing are described in Section 4.5.2.

On TD 15, subjects will have the following evaluations performed: brief physical exam, AE and concomitant medication assessment, and a skin biopsy obtained approximately 24 hours after administration of the last dose of study drug.

On TD 16, subjects will have the following evaluations performed: AE and concomitant medication assessment, safety laboratories, immunogenicity sampling, and PK sampling (approximately 48-hour post dose 5).

On TD 21, subjects will have the following evaluations performed: full physical examination, AE and concomitant medication assessment, post-treatment thermoregulation assessment, safety laboratories and PK sampling (approximately 168-hour post dose 5).

The remainder of the study procedures through Month 6 are described in the post-treatment section, Section 3.1.6.

Dose escalation in XLHED neonate cohorts will not occur until a review of safety and PK data from prior XLHED neonate cohorts has been completed by the DSMB, approximately three weeks after the last subject is dosed in each previous cohort. Assuming no safety or PK concerns following DSMB review, subjects in XLHED neonate cohort 2 will be dosed with EDI200 at 10 mg/kg/dose IV, a pharmacologic half-log increase. Subjects in XLHED neonate cohort 3 will be dosed with EDI200 at 30 mg/kg/dose IV. As part of the safety-monitoring program, prior to dosing subjects in each neonate cohort the DSMB will have reviewed safety and PK data from adults in the Phase 1 adult XLHED study where subjects received EDI200 at 3 and 10 mg/kg/dose in a similar dosing regimen (5 doses total at 2 doses/week).

3.1.6 *Post-Treatment Follow Up*

The post-treatment visits at Months of Life 2, 4 and 6 are designed to capture safety, immunogenicity and PD/efficacy data at appropriate timepoints following study drug exposure. In addition, PK data will be collected at Months of Life 2 and 6 visits. The post-treatment frequency of visits to the study site represents a balance between the acquisition of informative data and minimizing the travel stresses for the infant subject and his family. These evaluations will not supplant the subject's normal well-child care visits and immunizations by his primary care provider.

At Month 2 of life, subjects will have the following evaluations: full physical exam, AE and concomitant medication assessment, safety laboratories, PK and immunogenicity sampling, and PD/efficacy evaluations including growth and development and induced sweating. Expected stay at the study site location (i.e. within the vicinity of the study site) is 1-2 days.

At Month 4 of life, subjects will have the following evaluations: full physical exam, AE and concomitant medication assessment, and PD/efficacy evaluations including growth and development. Expected stay at the study site location (i.e. within the vicinity of the study site) is 1-2 days.

At Month 6 of life, subjects will have the following evaluations: full physical exam, AE and concomitant medication assessment, safety laboratories, PK and immunogenicity sampling, and PD/efficacy evaluations including growth and development, induced sweating and sweat duct imaging, dry eye assessment and digital facial photographs. Expected stay at the study site location (i.e. within the vicinity of the study site) is 1-2 days.

The conclusion of the core study is defined as the last visit of the last participant.

3.2 XLHED-Affected and Unaffected Male Siblings of Study Subjects

All male siblings (including multiple male siblings of a single neonate) of enrolled XLHED-affected neonates will be offered the opportunity to participate in a non-treatment, non-invasive evaluation providing historical control data for this open-label study. The technologies involved will be modeled on the core study evaluations, with the exception that no X-rays will be taken; no blood draws and no tissue sampling will be involved. The evaluations will take place at the study site and will include Informed Consent and Assent, if applicable, medical history, physical examination, vital signs including weight and height, digital facial photographs (frontal and lateral), growth and development assessments, induced sweating and sweat duct imaging, pulmonary function testing and eNO levels when age-appropriate (see Time & Events Schedule), dry eye evaluation and dental examination. Siblings will be asked to provide copies of their most recent dental radiographs. Expected stay at the study site location (i.e. within the vicinity of the study site) is 1-2 days.

3.3 Study Subjects

This Phase 2 study will enroll 9-15 XLHED-affected male neonates for study drug administration, and includes the optional enrollment of all male siblings, both affected and unaffected, for non-invasive evaluations.

3.3.1 *Inclusion Criteria*

Subjects for study drug administration must meet all of the following criteria to be enrolled:

1. Male with genetic confirmation of an XLHED diagnosis.
2. Subject must be at least 48 hours age and no older than 14 days.
3. Subject will have reached term (defined as 37 weeks gestation or older) prior to receiving first dose study drug.
4. Written informed consent of both parents (if reasonably available) must be obtained for treatment of their XLHED-affected male infant.
5. Neither mother nor the XLHED-affected male infant known to have received an investigational study drug in the 9 months prior to study subject enrollment in this study.
6. No major medical issues that the PI considers a contraindication to participation.

Male siblings of subjects receiving study drug must meet all of the following criteria to be enrolled in the natural history sub-study (no age limit involved):

1. Provide written informed consent/assent.
2. A full or half-sibling of a study subject where the study subject has received at least one dose of study drug in the Phase 2 XLHED Neonate Study and has not yet completed the study.
3. No major medical issues that the PI considers a contraindication to participation.

3.3.2 *Exclusion Criteria*

Subjects for study drug administration who meet any of the following criteria cannot be enrolled in this study:

1. Medically significant postnatal complications or congenital anomalies outside of those considered associated with the diagnosis of XLHED.

Male siblings of subjects receiving study drug who meet any of the following criteria cannot be enrolled in the natural history sub-study:

1. Known hypersensitivity to pilocarpine or pilocarpine-like muscarinic agonists.
2. Known hypersensitivity to lidocaine or lidocaine-like agents.
3. Presence of pacemaker.
4. Subjects who are not able or are not willing to comply with the procedures of this protocol.
5. Subject has a condition, which in the opinion of the PI would not allow for safe conduct of the study.

3.3.3 *Withdrawal or Removal of Subjects from the Study*

Study subjects/guardians may elect to discontinue study subject participation and withdraw from the study at any time without prejudice. The PI or Sponsor may withdraw a subject from participation in this study for any of the following reasons:

- A protocol violation occurs,
- The subject is not compliant with study procedures,
- A serious or intolerable adverse event occurs,
- The Sponsor or PI terminates the study, or
- The subject/guardian requests to be discontinued from the study.

A discontinuation occurs when an enrolled subject ceases participation in the study prior to completion of the protocol, regardless of the circumstances. The PI will determine the primary reason for discontinuation, and it will be recorded in the case report form and in the subject's research record. A discontinuation must be reported immediately to the Sponsor if it is due to a serious adverse event. The PI will provide or arrange for appropriate follow-up for such subjects (if required), and document the course of the subject's condition. In all cases of subject discontinuation, an attempt should be made to obtain the End-of-Study evaluations at their last study visit.

3.3.4 *Subject, Cohort or Study Suspension/Termination*

The Sponsor and/or the DSMB have the right to close this study at any time for safety or administrative reasons, although this should occur only after consultation between involved parties. The IRB/IEC and all relevant local National Competent Authorities must be informed.

3.3.5 *Subject Stopping Criteria*

- All AE and safety laboratory results will be available to the Medical Monitor, PI and DSMB in real time.
- For any Grade 2 or 3 adverse event (AE) defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v4.0; Appendix 2) that is deemed possibly, probably or definitely related to study drug treatment, individual subject dosing will be held pending review and recommendations of the Medical Monitor.
- If a subject misses a single dose and then is restarted, that dose will not be made up but all subsequent doses will be administered on schedule.
- If a subject misses two consecutive doses then dosing will not be restarted, but all study follow-up visits will occur as originally scheduled.

3.3.6 *Cohort Stopping Criteria*

The study design has only one cohort being dosed with study drug at any given time. Dosing of all subjects within a cohort will be suspended for:

- Two or more individuals develop a Grade 2 or 3 AE in a similar system organ class deemed possibly, probably or definitely related to study drug treatment (CTCAE v4.0), or
- For any Grade 4 adverse event (classified as severe or life-threatening) or a serious adverse event (SAE), regardless of drug-relatedness.

In the case where cohort dosing has been suspended, DSMB review of the AEs with the Medical Monitor, study PI and Sponsor will be required prior to discussing with a subject's family the option of restarting study drug or to enrolling additional subjects in the cohort. Missed doses will not be made up. Any subject missing two consecutive doses will not be restarted on treatment, will not be considered to have completed the dosing regimen, but will have all study follow-up visits as originally scheduled. If the DSMB safety review concludes that cohort dosing may continue, an additional subject may be added to the cohort for each subject that does not complete the dosing regimen.

In the case where a DSMB safety review concludes that a cohort should not continue dosing, no additional doses will be administered to subjects in that cohort, no additional subjects will be enrolled in that cohort, and all follow-up visits for enrolled subjects will occur as originally scheduled. The Sponsor will notify both the relevant National Competent Authorities and the local IRB/IEC of the action taken. The scheduled dose escalation cohorts will be suspended, although a more conservative dose escalation strategy may be considered for a subsequent cohort, requiring DSMB, relevant National Competent Authorities and study site IRB/IEC approval.

3.3.7 *Study Stopping Criteria*

The Sponsor and/or the DSMB have the right to close this study at any time for safety or administrative reasons, with timely notification of the relevant National Competent Authorities.

Permanent halting of dosing in any cohort by the DSMB related to safety concerns will trigger an automatic review of study termination by the DSMB in communication with the Medical Monitor, study PI, and Sponsor. If it is determined that study dosing should be terminated, all follow-up visits will occur as originally scheduled for subjects having received one or more doses of study drug. Study Sponsor assumes responsibility for reporting premature study termination to all regulatory authorities and institutional review boards.

Should the study be closed prematurely, all study materials (except documentation that has to remain stored with the PI) must be returned to the Sponsor. The PI will retain all other documents until notification given by the Sponsor for destruction.

3.3.8 *Treatment*

EDI200 study drug will be provided as a sterile solution for intravenous infusion in 3 ml glass vials, approximately 2.1 ml/vial at a concentration of approximately 5 mg/ml. Vials will be labeled according to local regulations and Sponsor standards. All study drug supplies should be stored frozen at -60 °C to -90 °C.

Dosing of EDI200 will vary by cohort. Study drug administration will be as follows:

Cohort	Number of subjects	Dose	Number of Doses	Study Day of Administration
Cohort 1	3-7	3 mg/kg	5	0, 4, 7, 11, 14
Cohort 2	3-7	10 mg/kg	5	0, 4, 7, 11, 14
Cohort 3	3-7	30 mg/kg	5	0, 4, 7, 11, 14

The weight used to calculate study drug dose will be the subject's Baseline weight for all doses. If during the treatment period a subject experiences a change in weight of >10% from Baseline, the PI(s) and the Medical Monitor will review the option of adjustments to the subject's dosing.

EDI200 will be **thawed to room temperature** on the day of dosing, pooled in syringe(s) and administered via a syringe pump infusion system. The study drug shall be administered by slow IV infusion over at least 30 min, not to exceed 5 ml/kg/hour or 8.5 mg/min EDI200, in order to minimize the risk of infusion-related AE (refer to Investigational Brochure, Section 6.2). For more information on the preparation of EDI200 see the Pharmacy/Investigator Manual.

Examples are shown in the table below.

Subject Weight	EDI200 Dose (mg/kg)	Total Dose EDI200	EDI200 Conc (mg/ml)	Vol	Vol/kg	Minimum Infusion Time	ml/kg/ hr	EDI200 mg/min
3 kg	3	9 mg	5	1.8 ml	0.6 ml/kg	0.5 hrs	1.2	0.3
3 kg	10	30 mg	5	6 ml	2.0 ml/kg	0.5 hrs	4	1.0
3 kg	30	90 mg	5	18 ml	6.0 ml/kg	2 hrs	3	0.75
4 kg	3	12 mg	5	2.4 ml	0.6 ml/kg	0.5 hrs	1.2	0.4
4 kg	10	40 mg	5	8 ml	2.0 ml/kg	0.5 hrs	4	1.3
4 kg	30	120 mg	5	24 ml	6.0 ml/kg	2 hrs	3	1.0
5 kg	3	15 mg	5	3 ml	0.6 ml/kg	0.5 hrs	1.2	0.5

5 kg	10	50 mg	5	10 ml	2.0 ml/kg	0.5 hrs	4	1.7
5 kg	30	150 mg	5	30 ml	6.0 ml/kg	2 hrs	3	1.25

During study drug administration and for 24 hrs following infusion the subject will have continuous heart rate and respiratory rate monitoring. A full set of vital signs including temperature, blood pressure, heart rate and respiratory rate will be documented on the following schedule:

- Pre dosing - a single set of vital signs within 1 hour of initiating dose infusion
- Post dosing:
    - 15 min after end of infusion,
    - 1 hr and 4 hrs after end of infusion,
    - then q4 hrs up to 24 hrs after end of infusion

If the unit in which the subject is receiving study drug requires additional monitoring, then that data will be added to the subject's record.

The intravenous site will be assessed for patency and signs of local irritation prior to the start of the infusion, every 30 minutes during infusion, and at the end of study drug infusion.

Doses 2-5 are scheduled for study days 4, 7, 11 and 14 respectively in all cohorts. If the subject is unable to be dosed on the specified day, a window of $\pm$24 hours is acceptable. However, there must be a minimum of two days between any two doses. The calendar date and 24-hour clock time of the beginning and end of each infusion will be recorded on the CRF. The dates and timing of PK sampling around dose 5 will be adjusted for any change in dosing schedule.

It is the responsibility of the clinical investigator to ensure that all study drug received at the site will be inventoried and accounted for throughout the study. Study drug must be handled strictly in accordance with the protocol and the container label and will be stored in a limited access area under appropriate environmental conditions. The investigator agrees neither to dispense the study drug from, nor store it at any site other than the study site locations agreed upon with the sponsor. Study drug should be dispensed under the direction of the investigator.

Study drug will be supplied only to subjects participating in the study. Study drug may not be relabeled or reassigned for use to other subjects. The dispensation and use of study drug must be documented on the Drug Accountability Form. Used and unused study drug must be available for verification by the sponsor's site monitor during on-site monitoring visits. The destruction or return to the sponsor of used or unused study drug will be approved by the sponsor and documented on the Drug Return Form.

4 STUDY EVALUATIONS

4.1 Medical Questionnaires

Two questionnaires are provided - one designated for the mother and XLHED-affected neonate (Appendix 3) and one designated for male siblings of an enrolled neonate (Appendix 4). The former includes family history related to XLHED, pregnancy, labor and delivery, and neonatal data. The latter includes general medical history with an emphasis on issues common to XLHED-affected males. This questionnaire will be used for both affected and unaffected male siblings.

4.2 Pharmacodynamic/Efficacy Evaluations

Assessment of PD/efficacy endpoints will be performed on all subjects. The Sponsor will provide any equipment and training required for assessments.

4.2.1 *Growth and Development*

Cross-sectional data in patient populations with hypohidrotic ectodermal dysplasia consistently reports poor growth in infancy, most commonly poor weight gain and feeding issues, and an elevated risk of abnormal development (Clarke et al., 1987; Motil et al., 2005; Blüschke et al., 2010). The growth assessments will consist of feeding history as well as measurements of weight, length, and head circumference taken at study visits as part of the physical examination and plotted on standardized growth curves for males. The initial physical examination will include assessment of standard developmental milestones, and will be augmented at Months 2, 4 and 6 by a validated, standard of care infant assessment tool. Examples of such tools include but are not limited to the Bayley Scales of Infant Development II (BSID-II) and III (BSDI-III) and the Denver Development Screening Test II (DDST II) (Black and Matula, 2000). Whichever tool is selected should be designed for down to age 2 months of life and should be used for all follow-up visits.

4.2.2 *Thermoregulation*

XLHED-affected neonates and infants have a well-documented abnormality of thermoregulation (heat intolerance) and as a consequence are at elevated risk for life-threatening hyperthermia under unmonitored conditions (Clarke et al., 1987; Blüschke et al., 2010). At present there are no validated genetic, clinical or physiologic markers that identify the level of risk for a given XLHED-affected patient. In this protocol, assessment of thermoregulatory risk for an XLHED-affected neonate will provide valuable information for the family in preparing for a safe transition to home. Additionally, demonstration in the long-term extension study of an improved and sustained thermoregulatory improvement may be a key efficacy element in the response to study drug. Thus it is a relevant and appropriate

evaluation in this protocol to assess thermoregulation of study subjects under closely monitored conditions with direct physician observation.

Thermoregulation reflects both sweat and insensible losses from the respiratory tract, both organ systems with compromised function in XLHED (Chawla et al., 2008; Clarke et al., 1987; Zankl et al., 2001; Casal et al., 2007; Seeliger et al., 2005). For term newborns placed inside a heated isolette, there is a wealth of validated clinical data on how to perform thermoregulation studies safely and what are the normal response parameters (e.g. Hey, 1975; Sjors et al., 1997; Stothers and Wagner, 1984; Sulyok et al., 1976). Healthy term babies reach the point of having to sweat to maintain body temperature at an isolette temperature of approximately 34°C. For thermoregulation assessment the study subjects will be placed unbundled in an isolette at a starting temperature of no more than 33°C in the ICU with continuous vital sign monitoring including respiratory rate, heart rate and body temperature. Isolette temperature will be held at the starting temperature for 0.5 hours for initial adaptation and baseline vital signs, following which it will be raised stepwise by 1-1.5°C every 30 minutes until reaching 36.5°C to assess infant response (Rutter and Hull, 1979). Total observation time is anticipated to be no more than 3 hours.

Strict stopping criteria will be in effect including: (1) a body surface temperature of ≥37.9°C (Rutter and Hull, 1979); (2) a noticeable change in behavior, e.g. uncontrolled crying; or (3) a sustained heart rate or respiratory rate outside of the normal range (HR 120-160 per minute; respiratory rate 40-60 per minute; Cloherty et al. 2004). With any of these changes or at the discretion of the study physician monitoring the assessment, the subject will be removed from the isolette to an unheated observation table until all vital signs and physical examination return to Baseline. Additional interventions are not anticipated, but will be at the discretion of the monitoring physician and the ICU staff.

In this exploratory endpoint, each subject's pre-dosing response to this short and controlled environmental challenge will be compared with the published literature and with the result of thermoregulation assessment after EDI200 dosing. Additional assessments of thermoregulation and heat tolerance are not standardized for ages 2-6 months but will be included as efficacy endpoints in the long-term extension study.

4.2.3 *Eccrine Structures*

4.2.3.1 Sweat Duct Density

Sweat duct density (number/cm^2) from at least two different sites on the soles of the feet (newborns and infants) or palms (siblings age ≥1 year) will be determined through analysis of images collected by direct visualization with an approved device, the Lucid VivaScope 1500 (www.lucid-tech.com). This technology has been tested in controls and XLHED-affected males from the newborn period to adulthood without complication (Dietz et al., 2013; Huttner et al., 2012; ECP-005 Clinical Study

Report). An adhesive ring will be placed on the subject's palm/sole to which the VivaScope will be attached via a magnetic lock. A series of photographs will be taken of an area approximately 6mm X 6mm. An individual trained in the use of this device will be involved in the acquisition of all images.

Up to two independent image readers trained in the reading of VivaScope images will interpret the images and provide sweat duct counts for inclusion with the study data. If there is a discrepancy in their counts of 10% or greater on an individual image, then both readers will reinterpret the same image and a final assessment made as an average of the repeat sweat duct counts. To account for growth during the study, all sweat duct counts will be adjusted for body surface area (Haycock et al, 1978).

4.2.3.2 Sweat Rate Testing

Sweat rate assessment following cholinergic stimulation is a technique used commonly in clinical trials as reported for the evaluation of distinct conditions including orthostatic hypotension, diabetes, growth hormone deficiency, Parkinson's disease, hypohidrosis, and Fabry's disease (Itoh et al., 2003; Low et al., 1983; Ramaswami et al., 2007). Maximal sweating on the volar lower arm surface of each subject will be induced by pilocarpine iontophoresis followed by sweat collection using the Macroduct Sweat Collection System developed primarily for sweat collection and analysis in the diagnosis of Cystic Fibrosis from the newborn period on (www.wescor.com). The Collection System consists of the Webster Sweat Inducer, Pilogel® Iontophoretic Discs and Macroduct Sweat Collectors. The Macroduct Sweat Collection System is approved for subjects of all ages including neonates (Mastella et al., 2000) and the manufacturer provides adequate directions for the device's use.

Pilogel® Iontophoretic Discs are unique gel reservoirs of pilocarpinium ions that are simple and safe to use in the iontophoretic stimulation of sweat. A Pilogel® disc is inserted into each of the recessed stainless steel electrodes, which are then attached to the subject. The Webster Sweat Inducer is activated by a start switch subsequently delivering a safe and optimal quantity of pilocarpine for gland stimulation (equivalent to five minutes iontophoresis at 1.5 mA) followed by an automatic, programmed stop.

Following completion of the pilocarpine iontophoresis the Webster Sweat Inducer electrodes and discs are removed from the subject, the application site is wiped once with alcohol, and a Macroduct Sweat Collector is placed over the site of one electrode. The Macroduct Sweat Collector is held in place for approximately 30 minutes using a Velcro Macroduct Strap. Sweat volume is determined from microliter markings on a collection coil diagram.

Individuals trained in the use of the Macroduct Sweat Collection System will be involved in both procedures and the acquisition of the data. The manufacturer of the iontophoresis device does report the rare occurrence (1 in 50,000) of small skin burns at the site of application, and physicians will be available on site to evaluate any adverse event occurrence.

4.2.4 *Pulmonary Function Testing and eNO levels*

Pulmonary function testing will be performed in the sibling sub-study on all subjects age 5 years and older at a laboratory experienced with pediatric subjects. Additionally, levels of exhaled nitric oxide (eNO) as an indicator of pulmonary inflammation will be quantified non-invasively with an age-group appropriate device in all siblings age 4 years and older.

4.2.5 *Dry Eye Assessment*

The eye examination will be performed by an ophthalmologist experienced in assessments of tear film and ocular surface in infants as well as children and adults. In newborns and infants, the examination will document the presence/absence of signs of infection and irritation, as well as a tear film break-up time. For children 5 years or older (sibling sub-study) the assessment will also include the Shirmer test for rate of tear production and the OCULAR SURFACE DISEASE INDEX© questionnaire (Appendix 5).

4.2.6 *Skin Biopsy*

Three mm diameter punch biopsies of skin will be obtained from the upper outer thigh area. Sites will follow their institutions standard practice with regard to biopsy procedure. The biopsy site may require absorbable suture(s). RNA isolated from the skin biopsies will be assayed in expression analyses to establish a biochemical response to EDI200 treatment in these EDA-deficient subjects. Genes to be evaluated include but are not are not limited to those involved in the EDA/EDAR pathway, e.g. EDAR, CTGF (connective tissue growth factor), Shh (sonic hedgehog) and Lgr5 (leucine-rich G-protein coupled receptor). For each study subject, comparisons will be made between the expression profiles obtained at Baseline, after the first and the last dose of EDI200.

4.2.7 *Dental Imaging/Examination*

The absence of tooth buds is a key confirmatory finding in phenotype assessment of an XLHED-affected neonate and can be determined from a lateral radiograph (Swischuk, 2003). Radiation exposure will be minimized in this study with a single lateral film at Baseline. Follow-up radiographs will be included in the long-term extension study for PD/efficacy documentation (first follow-up expected at age 2 years). Radiographs are the preferred

imaging modality as they detect tooth bud mineralization but do not require sedation in the infant.

The sibling sub-study includes a dental examination that is brief and age-appropriate involving an assessment of tooth count and tooth shape. No X-ray exposure will be involved.

4.3 Genetic Testing

To meet inclusion criteria for EDI200 administration, potential study subjects are required to have their XLHED diagnosis confirmed by genetic testing of the EDA gene and these test results relayed to the study site. EDA genetic testing itself is outside of the scope of this protocol. If requested, the families of prospective subjects in need of EDA genotyping will be referred to resources available to facilitate this testing. Consent from the family (written or verbal) will be obtained as part of the screening process to provide the study site with documentation of genetic testing results via a secure and confidential method including an option for electronic transmission.

It has been demonstrated that a polymorphism in the EDAR gene associated with increased activity may be associated with amelioration of some XLHED-symptoms (Cluzeau et al., 2012). As this has the potential to impact outcome measures, all participating neonates will be tested for this specific polymorphism, c.1540T>C, rs3827760, p.V370A. The testing may be performed on the prior DNA sample used for EDA genotype confirmation, although results are not required prior to the initiation of dosing.

4.4 Digital Facial Photographs

A facial recognition software algorithm is under development that will identify characteristics of XLHED-affected males as neonates, children and adults. The algorithm uses non-invasive 2D frontal photographs and will be used in this study to document the newborn facial appearance as well as changes in craniofacial appearance over time, including the long-term extension study. Facial frontal and lateral digital images will be obtained with a commercial camera, and all photographs will be anonymized prior to transmission for analysis to FDNA, the company developing the software algorithm (http://www.fdna.com).

4.5 Clinical and Safety Laboratory Evaluations

4.5.1 *Safety Laboratory Sampling*

Laboratory parameters measured at the study site will include a complete blood count (RBC, WBC, hemoglobin and hematocrit) with differential and platelet count, serum chemistries including glucose, electrolytes (Na, K, Cl, Ca), total protein and albumin, assessment of hepatic and renal function (BUN, serum creatinine, AST, ALT and alkaline phosphatase), and urinalysis (dipstick and microscopy). It will be the Principal Investigator's responsibility to assess laboratory parameters against local reference ranges and to assess the clinical significance of any out-of-range values.

4.5.2 *Pharmacokinetic Sampling*

Analysis will be performed to characterize EDI200 PK after the doses designated as dose #1 and #5. Blood samples (0.25 ml) for determination of EDI200 in plasma will be taken into collection tubes without additives on the days and times indicated. The model used to determine frequency of pharmacokinetic sampling incorporates a sparse sampling approach in order to reduce the number of blood samples required for each subject. Note that additional PK samples are scheduled for age 2 and 6 months to assess study drug persistence at low levels as was reported for XLHED adults.

PK samples will be drawn at approximately the following time points pre-dose (defined as prior to the start of infusion) and post-dose (defined as after infusion is completed):

	Pre-Dose	Post-Dose							
		15 (±5) min	3 (±.5) hrs	8 (±1) hrs	18 (±2) hrs	24(±2) hrs	48 (±4) hrs	168(±8) hrs	Age 2 months (±1 wk) & 6 months (±2 wks)
D0 (dose 1)	X	X	X	X		X	X		
D14 (dose 5)	X	X	X		X		X	X	X

Immediately upon sampling, the sample will be identified with a label bearing details of the study number, subject number, sampling time point, and a sample type. The sample will be separated by centrifugation at rotation 1500xg, 4°C for 10 minutes. Two 50 ul aliquots of serum will be transferred to polypropylene tubes labeled identically to the original blood sample and stored at approximately -70°C pending analysis. The time at which samples are taken, received into the separating room and placed in the freezer will be recorded in the study documentation.

4.5.3 *Immunogenicity Sampling*

Blood samples (~0.25 mL per sample) for immunogenicity sampling will be taken into serum separator tubes on the days indicated.

Immediately upon sampling, the sample will be identified with a label bearing details of the study number, subject number, sampling time point, and a sample type. The sample will be separated by centrifugation. Two equal aliquots of serum will be transferred to polypropylene tubes labeled identically to the original blood sample and stored at approximately -70°C pending analysis. The calendar date and 24-hour clock time at which samples are taken, centrifuged and placed in the freezer will be recorded in the study documentation.

4.5.4 *Total of Blood Volume*

The approximate number of safety laboratory evaluations and the approximate volume of blood that will be collected per subject throughout the study are as follows:

All Subjects	Genetic Testing (5 ml)*	Safety Labs (1.5 ml)	Immunogenicity (0.25 ml)	PK (0.25 ml)	Total Blood Volume (ml)	ml/kg (3.5 kg neonate)
Screening	0	0	0	0	0.00	
Baseline	1 x 5 = 5.0	1 x 1.5 = 1.5	1 x 0.25 = 0.25	0	6.75	1.93
Week 1	0	1 x 1.5 = 1.5	0	6 x 0.25 = 1.50	3.00	0.86
Week 2	0	0	0	0	0	0
Week 3	0	1 x 1.5 = 1.5	1 x 0.25 = 0.25	5 x 0.25 = 1.25	3.00	0.86
Week 4	0	1 x 1.5 = 1.5	0	1 x 0.25 = 0.25	1.75	0.50
Months 2,4,6	0	2 x 1.5 = 3.0	2 x 0.25 = 0.50	2 x 0.25 = 0.50	4.00	
Total	1 x 5 = 5.0	6 x 1.5 = 9.0	4 x 0.25 = 1.0	13 x 0.25 = 3.25	18.25	

* For testing of the EDAR polymorphism in the case that DNA is not available from prior genotyping

4.6 Safety Evaluations

The safety evaluations will consist of adverse events, concomitant medications, vital signs, weight, physical exam findings, and safety laboratory values. Adverse events will be recorded starting when the treatment Informed Consent document (ICF2) is signed and continuing until all study assessments are completed (including Month 6 follow-up evaluations for all AEs, and Month 6 + 28 days for SAEs). Information on the definition, characteristics, and reporting requirements are provided below.

4.6.1 *Adverse Events*

4.6.1.1 Definition

An adverse event (AE) is any reaction, side effect, or other untoward event (signs, symptoms, or changes in laboratory data) associated with participation in this study, whether or not the event is considered related to the study or any of the procedures being conducted. All AEs occurring after signing the informed consent document will be recorded. AEs will be ascertained on the basis of volunteered symptoms and clinical observation. AEs will be

recorded during the study on the appropriate CRF page. All AEs considered to be related to study procedures, and all serious adverse events (SAEs; see Section 4.5.2) will be followed until resolved or until a stable status has been achieved. SAEs will be recorded up to 28 days following the Day 168 visit.

4.6.1.2 Reporting Adverse Events

Any adverse event (AE, a clinical sign, symptom, or disease) temporally associated with this study, whether or not considered related to study drug, shall be documented on the case report form (CRF). All AEs reported by the subject or observed by the PI will be individually listed. The signs and symptoms, the date of onset, duration, and relationship to study drug, action taken, and follow-up procedures will be reported.

4.6.1.3 Relationship

The relationship between an AE and the administration of study drug or the procedures employed in this study will be determined by the PI on the basis of his or her clinical judgment and the following definitions:

Definitely Related: Follows a reasonable temporal sequence from administration of study drug; follows a known response pattern to the study procedure; and, when appropriate to the protocol, is confirmed by improvement after stopping the study procedure (positive re-challenge) and by reappearance of the reaction after repeat exposure (positive re-challenge); and cannot be reasonably explained by known characteristics of the participant's clinical state or by other therapies.

Probably Related: Follows a reasonable temporal sequence from administration of study drug; follows a known response pattern to the study procedure; and, when appropriate to the protocol, is confirmed by improvement after de-challenge; and cannot be reasonably explained by the known characteristics of the participant's clinical state or by other therapies.

Possibly Related: Follows a reasonable temporal sequence from administration of study drug and follows a known response pattern to the study procedure but could have been produced by the participant's clinical state or by other therapies.

Unlikely Related: The reaction has little or no temporal sequence from administration of the study drug, and/or a more likely alternative etiology exists.

Not Related: Sufficient information exists to indicate that the etiology is unrelated to administration of study drug in this study. Two or more of the following variables apply:

- The AE does not follow a reasonable temporal sequence with occurrence of administration of study drug;

- The AE is readily explained by the participant's clinical state or other therapies.

4.6.1.4 Severity

The intensity of an AE, as determined by the PI, will be assessed and graded utilizing a 5-point scale according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v4.0). It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under section 4.6.2. If a subject experiences the same AE with more than one level of intensity, the highest level of intensity should be recorded on the CRF. The severity grading will be reported in the eCRF as follows:

Grade 1 = **Mild;** asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 = **Moderate**; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
Grade 3 = **Severe** or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
Grade 4 = **Life-threatening** consequences; urgent intervention indicated.
Grade 5 = **Death** related to AE.

4.6.1.5 Outcome

The outcome of an AE will be assessed as follows:

- Resolved
- Unresolved
- Resolved with sequelae
- Death
- Unknown

4.6.2 *Serious Adverse Event*

4.6.2.1 Serious Adverse Event Definition

An SAE is any AE that results in any of the following outcomes:

- Death
- A life threatening AE
  - The term "life-threatening" means that the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe
- An inpatient hospitalization or prolongation of existing hospitalization (24 hours or more)

- A persistent disability/incapacity, or a
- A congenital anomaly/birth defect
- Important medical event

An important medical event may not result in death, be life threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

4.6.2.2 Serious Adverse Event Reporting

The PI will report all SAEs to the Sponsor in a timely fashion, within 24 hours of awareness, by completing and faxing the SAE Report Form to CTI Safety as per directions described in the Study Reference Manual. The reporting PI is obligated to provide their initial assessment of the relationship between study drug and the occurrence of each SAE. Determination of expectedness and the reporting of the SAEs to relevant regulatory authorities will be determined by the Sponsor. The reporting PI is responsible for reporting all SAEs to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) as required by the appropriate regulations.

Based on the investigator's assessment of causality of the adverse event and discussions with the medical monitor, a decision will be made by the sponsor concerning the need for further action with respect to the future conduct of this trial. The primary consideration governing further action is whether new findings affect the safety of other subjects participating in the clinical study. If the discovery of a new adverse event related to study drug raises concerns over the safety of its continued administration to subjects, the sponsor or designee will take immediate steps to notify the Data Safety Monitoring Board (DSMB), the regulatory authorities and all the investigators participating in clinical studies of the study drug.

The Sponsor will notify the relevant regulatory authorities according to Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) regulations. The reporting PI will notify the Sponsor through the following contact:

Name:	CTI Global Drug Safety & Pharmacovigilance
Address:	10123 Alliance Road Cincinnati, OH 45242
Telephone:	1-877-755-0742
Fax:	1-866-215-5862
E-mail:	CTISafety@ctifacts.com

Additional SAE follow-up information, if required, should all be faxed to CTI Safety within 24 hours of receipt. The follow-up information should be documented on the original SAE Report Form following Good Documentation Practices and faxed with any additional relevant source

documentation. Additionally, the AE eCRF should be updated accordingly to match the SAE Report form.

SAE source documentation requested may include; discharge summary, diagnostic test results, consultation reports, relevant specimen cultures, diagnostics, or laboratory values. The investigator must ensure that all source documentation maintains each subject's anonymity. The site and subject number must be documented on every page, the subject's name replaced by the subject's study number, and all other protected health information should be redacted (e.g. social security number, medical record number, room number, etc.).

Compliance with the requirements for expedited reporting is essential. The sponsor or the sponsor's designee is responsible for informing the regulatory authorities as well as all other participating investigators of the following events:

- Any event associated with the use of the study drug, that is both serious and unexpected (SUSAR), or
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.

The sponsor or designee will expedite the reporting of all SUSARs to the appropriate regulatory authorities and the Institutional Review Board/Independent Ethics committee (IRB/IEC). The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse event (AE). For fatal or life threatening cases, the term will be a maximum of 7 calendar days for a preliminary report with another 8 calendar days for completion of the report. The sponsor or designee will also inform all investigators of such events.

The sponsor or designee will provide expedited reports of the following SUSARs to the IRB/IEC:

- SUSARs that have arisen in the clinical trial that were assessed by the EC
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that were assessed by the EC.

4.7 Concomitant Medication

There are no concomitant medications that are excluded from this study. There are no concomitant medications known to interact with EDI200.

4.8 Data Safety Monitoring Board (DSMB)

An independent DSMB will be established to monitor the safety of treated subjects. A European member has been added to the same DSMB in place for the Phase 1 adult safety

study (ECP-004) to monitor this neonate trial. All safety-related laboratory values will be available to the DSMB in real time. At the scheduled DSMB review meetings, detailed safety reviews will be provided to the DSMB including; adverse events, concomitant medications, infusion/injection site reactions, physical examination, weights and vital signs, and all PK and safety laboratory values. Scheduled DSMB meetings include the following:

- After dosing is completed in XLHED neonate cohort 1, the DSMB will meet and review safety and PK data from all cohort 1 subjects prior to initiation of dosing in XLHED neonate cohort 2. The timeframe for this review is approximately three weeks following dosing of the last cohort 1 subject. The cohort 1 PK data review is intended to confirm that the exposure levels in the cohort as a whole and for each subject were within the limits associated with safe study drug administration in the preclinical GLP toxicology studies, and that the expected exposure with dose escalation in cohort 2 will remain in the range that was safe and well tolerated. Additionally, the DSMB will review safety and PK data obtained from adult cohort 2 (NCT01564225, www.clinicaltrials.gov) dosed at the same 10 mg/kg/dose as is proposed for neonate cohort 2.
- After dosing is completed in XLHED cohort 2, the Sponsor may elect to enroll a third cohort with EDI200 dosing at 30 mg/kg/dose. Prior to initiating dosing of this third cohort, the DSMB will review safety and PK data from cohorts 1 and 2 in order to provide guidance on advancing to dosing at the higher level.
- At the end of the Study, DSMB will review and summarize all study safety data. DSMB summaries will be provided in a timely fashion to the Sponsor.

Unscheduled DSMB reviews will take place as outlined in Section 3.3.4-3.3.7 for single or accumulated adverse events. Additional safety-related evaluations of one or more subjects may be requested by the DSMB based on findings through the 6-month, end-of-study visit.

5 SCHEDULE OF STUDY ASSESSMENTS

5.1 Screening – End of first trimester through DOL #12

- Medical history related to XLHED in the family and for pregnancy, labor and delivery
- Verbal consent from both parents (if reasonably available) to provide documentation of genetic testing results to the study site by a secure and confidential method including the option for electronic transmission
- Inclusion/Exclusion criteria will be confirmed for parents and fetus/neonate

**A screening call may be conducted to assess eligibility for study participation, inclusion/ exclusion criteria, and availability of EDA genetic test results. If prior genotyping is not available, either cord blood or a neonatal blood sample may be sent to an accredited laboratory for testing.*

5.2 Baseline – DOL #2 through DOL #14

- Transport Informed Consent from both parents (if reasonably available) if neonatal transport to the study site is to be provided as part of the study
- Treatment Informed Consent from both parents (if reasonably available) for study procedures and study drug administration
- Confirmation of inclusion/exclusion criteria
- Updated medical history
- Full physical examination
- Blood draws for safety laboratories, EDAR gene V370A polymorphism testing, PK and immunogenicity
- Bioactivity assessments
    - Growth and development
    - Dental imaging
    - Digital facial photograph
    - Sweat duct density
    - Sweat rate
    - Dry eye assessment
    - Thermoregulation
    - Skin biopsy sample for molecular profiling
- Adverse Events & Concomitant Medications

5.3 Treatment

Day 0

- Brief physical exam (prior to dosing)
- Study drug administration (dose 1)
- Vital sign monitoring during and for 24 hours following study drug infusion
- Blood draw for PK analysis at the following timepoints:
    - Post-end of infusion timepoints: 15 min, 3 and 8 hours
- Adverse Events & Concomitant Medications

Day 1

- Brief physical exam
- Blood draw for safety laboratory evaluations
- Blood draw for PK analysis at the following timepoints:
    - 24 hours post dose 1
- Skin biopsy 24 hours post dose 1
- Adverse Events & Concomitant Medications

Day 2

- Blood draw for PK analysis at the following timepoints:
    - 48 hours post dose 1
- Adverse Events & Concomitant Medications

Day 4

- Brief physical exam (prior to dosing)
- Study drug administration (dose 2)
- Vital sign monitoring during and for 24 hours following study drug infusion
- Adverse Events & Concomitant Medications

Day 7

- Brief physical exam (prior to dosing)
- Study drug administration (dose 3)
- Vital sign monitoring during and for 24 hours following study drug infusion
- Adverse Events & Concomitant Medications

Day 11

- Brief physical exam (prior to dosing)
- Study drug administration (dose 4)
- Vital sign monitoring during and for 24 hours following study drug infusion
- Adverse Events & Concomitant Medications

Day 14

- Brief physical exam (prior to dosing)
- Study drug administration (dose 5)
- Vital sign monitoring during and for 24 hours following study drug infusion
- Blood draws for PK analysis at the following timepoints:
    - Pre-dose and the following post-end of infusion timepoints: 15 minutes, 3 and 18 hours
- Adverse Events & Concomitant Medications

Day 15

- Brief physical exam
- Skin biopsy for molecular profiling (24 hours after study drug administration)
- Adverse Events & Concomitant Medications

Day 16

- Blood draw for PK analysis at the following timepoints:
    - 48 hours post dose 5
- Blood draw for safety laboratory evaluations
- Blood draw for immunogenicity testing
- Adverse Events & Concomitant Medications

Day 21

- Full physical exam
- Blood draw for safety laboratory evaluations
- Blood draw for PK analysis at the following timepoints:
    - 168 hours post dose 5
- Thermoregulation assessment
- Adverse Events & Concomitant Medications

**If any visits are adjusted during the baseline and/or treatment portions of the study (if a subject is seen or dosed earlier or later than what is described in the protocol) then all subsequent visits (if applicable) should be adjusted accordingly.*

5.4 Post-Treatment

Follow-Up Visit 1 – Month of Life 2 (±1 week)

- Full physical exam
- Blood draw for safety laboratory evaluations
- Blood draw for immunogenicity testing
- Blood draw for PK
- PD/efficacy assessments
    - Growth and development

  - Sweat rate
- Adverse Events & Concomitant Medications

Follow-Up Visit 2 – Month of Life 4 (±1 week)

- Full physical exam
- PD/efficacy assessments
  - Growth and development
- Adverse Events & Concomitant Medications

End-of-Study Visit – Month of Life 6 (±2 weeks)

- Full physical exam
- Blood draw for safety laboratory evaluations
- Blood draw for immunogenicity testing
- Blood draw for PK
- PD assessments
  - Growth and development
  - Digital facial photographs
  - Sweat duct density
  - Sweat rate
  - Dry eye assessments
- Adverse Events & Concomitant Medications

5.5 Unscheduled Visits

The Sponsor or DSMB may request unscheduled visits either during the subject's participation in the Study or after his completion. The unscheduled visits may include additional safety-related evaluations (including blood sampling) based on findings through the 6-month, end-of-study visit.

6 STATISTICAL METHODS

6.1 Sample Size

The sample size is based on clinical and practical considerations for a Phase 2 study in an ultra-rare genetic disorder with enrollment limited to newborns. It is considered to be appropriate to meet the objectives of the study while minimizing the exposure of volunteers. Each cohort is anticipated to enroll approximately 3-7 XLHED-affected neonates. No more than 15 subjects total will be enrolled.

6.2 Analysis Datasets

The safety analysis set will consist of all subjects who receive at least one dose of study medication. The PK analysis set will consist of those subjects who receive at least one dose of study medication and have sufficient concentration data to obtain a plasma concentration by time profile. The PD/efficacy analysis set will consist of all subjects who receive at least one dose of study medication and complete the follow-up assessments through at least month 2. No missing data will be replaced by values carried forward.

6.3 Primary and Pharmacodynamic/Efficacy Assessments

The safety assessment variables are AEs, concomitant medications, vital signs, weight, physical examination findings, hematology, clinical chemistry, and urinalysis laboratory test results.

The PK assessment variables will be the following derived PK parameters for EDI200:

- C_{max}, T_{max}, $AUC_{0\text{-}tau}$
- Other PK parameters including but not limited to clearance rate may also be examined.

The medical history and clinical evaluations for the sibling sub-study will be tabulated and intra-familial comparisons will be made with data obtained from the neonate subjects receiving study drug.

The following pharmacodynamic/efficacy outcomes will be monitored in all subjects receiving study drug:

- Growth and development
- Dentition (follow-up radiographs in extension study)
- Craniofacial development by digital photography
- Sweat duct density
- Sweat rate
- Dry eye signs and symptoms
- Thermoregulation
- Molecular expression profile of skin biopsy tissue

6.4 Pharmacodynamic/Efficacy Variables (not including sibling sub-study)

Growth and Development
Testing to be performed at Baseline, Months of Life 2, 4, and 6:

- Weight, length, head circumference plotted on standardized growth curves for males
- Developmental assessments

Dental Imaging:
Testing to be performed at Baseline:

- Lateral jaw film

Craniofacial Development
Testing to be performed at Baseline, and Month of Life 6

- Digital facial photographs

Sweat Duct Density
Testing to be performed at Baseline and Month of Life 6:

- Sweat ducts per 36 mm^2 on confocal microscopy image

Sweat Rate:
Testing to be performed at Baseline, Months of Life 2 and 6:

- Volume of induced sweat collected over 30 minutes following pilocarpine iontophoresis

Dry Eye Assessments:
Testing to be performed at Baseline and Month of Life 6:

- Examination for signs of infection and/or irritation, as well as tear film break-up time

Thermoregulation
Testing to be performed at Baseline, TD21:

- Clinical and vital sign response to isolette temperature range

Skin Biopsy for Molecular Expression Profile:
Testing to be performed at Baseline, TD1 (approximately 24 hours after 1st dose) and TD15 (approximately 24 hours after last dose):

- Analysis of gene expression on skin biopsy samples

6.5 Analysis of Safety and Pharmacokinetic Variables

Safety variables will be tabulated and presented for all subjects receiving one or more doses of EDI200. Change from Baseline over time will be presented by cohort for continuous variables including laboratory values and vital signs using descriptive statistics with n, mean, standard

deviation, minimum, median and maximum as appropriate. Shift tables will be presented. Out-of-range values will be flagged in the data listings and will also be presented separately.

AEs will be coded using the current MedDRA drug dictionary version. Only treatment emergent AEs will be included in the summary tables. The incidence of subjects reporting AEs will be summarized by system organ class, preferred term, severity and relationship to study drug.

The PK parameters of EDI200 will be listed and summarized by dosing cohort. Mean and individual plasma concentration-time curves will be presented on both linear and semi-logarithmic scales. The derivation of the PK variables from the EDI200 plasma concentrations will be determined using WinNonlin Professional v5.2, or higher. The PK parameters of EDI200 will be listed and summarized.

6.6 Statistical Methods

Individual subject values for EDA genotype and all endpoints, both at Baseline and across time, will be provided. Demographics for the entire study dataset will be presented using descriptive statistics. Table summaries of Baseline values for all endpoints will be provided for the following groups: all subjects and each dosing cohort. Descriptive statistics will be provided across time for each cohort with n, mean, standard deviation, minimum, median and maximum as appropriate.

6.7 Data Management

As outlined in section 7.5 the Sponsor or designee will forward questions regarding missing data or discrepancies to the PI.

The original terms used in the case report forms by the PI to identify adverse events will be coded according to the MedDRA dictionary. The percentage of subjects with adverse events will be tabulated overall and by the MedDRA body system and preferred term.

7 STUDY ADMINISTRATION

7.1 Protocol Modifications

Neither the PI nor Sponsor will modify this protocol without obtaining the concurrence of the other. All protocol amendments must be issued by the Sponsor, signed and dated by the PI, and should not be implemented without prior IRB/IEC approval, except where necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study (e.g., typographical errors, inconsistencies).

In situations requiring a departure from the protocol, the PI or other physician in attendance will discuss with the appropriate Sponsor representative. This contact will be made before implementing any departure from protocol. In all cases, contact with the Sponsor will be made as soon as possible in order to discuss the situation and agree on an appropriate course of action. Any departure from the protocol and the circumstances requiring it will be documented.

7.2 Monitoring

The Sponsor or their designee (hereby referred to as “Monitor”) will monitor all aspects of the study as required by GCP and any existing standard operating procedures for compliance with applicable regulations. These individuals will have access to all records necessary to ensure integrity of the data and will review progress of the study with the PI.

The monitor will compare the data entered into the CRF’s with any source documents. The nature and location of any source documents will be identified in advance. This will ensure that all sources of original data required to complete the CRF are known to the Sponsor and investigational staff; and are accessible for verification by the Monitor. If electronic records are maintained, the method of verification must be discussed with the investigational staff. At a minimum, source documentation must be available to substantiate subject identification, eligibility and participation, proper informed consent procedures, adherence to protocol procedures, record of safety parameters, adequate reporting and follow-up of adverse events, completion and reason of withdrawal/ termination. Specific items required as source documents will be reviewed with the PI before the study. The author of an entry in the source documents will be identifiable.

If any data are recorded directly into the CRF, at a minimum there should be an entry in the source document that each of the assessments was done, and by whom and the date it was done. The author of an entry in the source documents must be identifiable. The CRF data will be entered into an appropriate data storage system and verified for accuracy.

Direct access to source documentation must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. Findings from this review

of CRF's and source documents will be discussed with the investigational staff. The Sponsor expects that, during monitoring visit(s), the relevant investigational staff will be available, the source documentation will be available, and a suitable environment will be provided for review of study-related documents. The monitor will provide feedback on the study conduct to the PI.

The investigator will permit trial-related monitoring, audits, audits, IRB/IEC review, and regulatory inspection(s), and providing direct access to source data/documents.

7.3 Ethic Aspects

7.3.1 PI Responsibilities

The PI is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines, Good Clinical Practice (GCP), and applicable regulatory requirements.

GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well being of study subjects are protected, consistent with the principles that have originated in the Declaration of Helsinki and that the clinical study data are credible.

7.3.2 Institutional Review Board/Independent Ethics Committee

The PI will provide the Institutional Review Board/Independent Ethics committee (IRB/IEC) with all requisite material, including a copy of the protocol, informed consent and all subject materials. The study will not be initiated until the IRB/IEC provides written approval of the protocol and the informed consent and the PI has obtained documents approved by the IRB/IEC. Any reports requested on the progress of this study by the PI will be made to the IRB/IEC and the Sponsor.

7.3.3 Informed Consent

A properly executed, written informed consent in compliance with national and local regulations and GCP guidelines will be obtained from each subject prior to entering the study or performing any study-related procedure.

The PI will submit a copy of the informed consent document to the IRB/EC for review and approval before research subjects are enrolled. The PI will provide a version of the signed informed consent to the subject and a signed version will be maintained in the subject's research record.

7.3.4 Confidentiality of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the safety, quality, and utility of the procedures performed during this study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

The Sponsor ensures that the personal data are:

- Processed fairly and lawfully
- Collected for specified, explicit, and legitimate purposes and not further processed in a way incompatible with these purposes
- Adequate, relevant, and not excessive in relation to said purposes
- Accurate and, where necessary, kept up to date

Explicit consent for the processing of personal data will be obtained from the participating subject before collection of data. Such consent should also address the transfer of the data to other entities and to other countries, if applicable.

The subject has the right to request through the PI access to his/her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps should be taken to respond to such request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel and designees whose responsibilities require access to personal data agree to keep the identity of study subjects confidential.

7.4 Subject Identification Register

The PI agrees to complete a subject identification register to permit easy identification of each subject during and after the study. The Monitor will review the document for completeness.

The subject identification register will be treated as confidential and will be filed by the PI in the Regulatory Binder. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by initials and assigned number only.

7.5 Case Report Form Completion

All of the clinical data will be captured via electronic data capture (EDC) using an approved and validated EDC system. The investigator site staff will enter and edit the data via a secure network, with secure access features (username, password and secure identification – an electronic password system). A complete electronic audit trail will be maintained.

The investigator will approve the data using an electronic signature, and this approval is used to confirm the accuracy of the data recorded (CFR 21, Part. 11, 2011).

Electronic CRF's (eCRF) will be used for all patients. The investigator's data will be accessible from the investigator's site throughout the trial. The eCRFs must be kept current to reflect patient status at each phase during the course of the trial. The patients must not be identified on the eCRF by name. The appropriate coded identification (i.e. Patient Number) must be used. The investigator must make a separate confidential record of these details (subject identification record) to permit identification of all patients enrolled in a clinical trial in case follow-up is required.

Copies of the eCRF together with all data changes made will be supplied to the investigator at the end of the trial. The investigator will be responsible for retaining all records pertaining to the trial as specified in the appropriate contract.

7.6 Data Quality Assurance

Steps to be taken to assure the accuracy and reliability of data include the selection of a qualified PI, review of protocol procedures with the PI and associated personnel before the study, and a monitoring visit(s) by the Sponsor. Instruction for completion of CRFs will be provided and reviewed with study personnel before the start of the study. The Monitor will review CRFs for accuracy and completeness during the conference and/or during a monitoring visit(s). Any discrepancies will be resolved with the PI or designee, as appropriate. The data will be entered into an appropriate data storage system and verified for accuracy.

7.7 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

APPENDIX 1 – AUTOMATIC PHENOTYPE IDENTIFICATION OF XLHED PATIENTS

FINAL REPORT

Provided as a separate document.

APPENDIX 2 – THE NATIONAL CANCER INSTITUTE (NCI) COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS V4.0 (CTCAE)

VERSION 4.0

US DEPARTMENT OF HEALTH AND HUMAN SERVICES- NATIONAL INSTITUTES OF HEALTH-NATIONAL CANCER INSTITUTE

Provided as a separate document.

APPENDIX 3 – MEDICAL QUESTIONNAIRE FOR MOTHERS AND XLHED-AFFECTED NEONATES

Medical Questionnaire for Mothers and XLHED-Affected Neonates

Participant's Initials: ☐☐☐ **Can be left blank if choice of name is not yet finalized*

Today's Date: ☐☐/☐☐/☐☐☐☐

Date of birth: ☐☐/☐☐/☐☐☐☐
DD/MM/YYYY

Has the mother been diagnosed with HED? ☐Yes ☐No

If yes, age at diagnosis: ☐0-5 years ☐6-17 years ☐≥18 years

Does the mother have any family members diagnosed with HED? ☐Yes ☐No

If yes, check all that apply:
☐Mother
☐Father
☐Sisters
☐Brothers
☐Aunts
☐Uncles
☐Other
If other, specify:

Has the mother or any family member(s) had genetic testing for HED? ☐Yes ☐No
**Every attempt should be made to obtain a copy of the genetic test results. The results must be provided to the study site and will also be provided to the lab conducting your baby's genetic testing in order to expedite the testing process.*

Mother's age at delivery: ☐☐

What number pregnancy is/was this child for the mother? ☐☐

Is the mother currently pregnant? ☐Yes ☐No

Thinking of *all* of the mother's pregnancies to date, including this one, how many resulted in each of the following:

	Number
Miscarriage in the first trimester (up to 14th week of pregnancy)	☐☐
Miscarriage later in pregnancy	☐☐
Stillbirth	☐☐
Preterm birth (prior to 37 weeks)	☐☐
Full term birth (37 weeks or more)	☐☐

Did the mother have any of the following complication during ***this child's*** (the study subject) pregnancy? ☐Yes ☐No

If yes, please list treatment.

Diabetes: _____
High blood pressure: _____
Infections, fevers and illnesses: _____
Other problems/complications: _____

Medications used during pregnancy: _____
_____
Are any of these medications investigational? ☐Yes ☐No

Did the mother have any of the following?
☐Ultrasound
☐1st trimester screen/triple/quad screen
☐Amniocentesis or CVS

Were any results from this testing abnormal? ☐Yes ☐No

If yes, please explain:
_____
_____

Check here ☐ if your child is not born yet and do NOT complete the rest of this form.

The child was born:
☐Full-term
☐Prematurely (weeks premature: ☐☐)

If premature, please list the reason:
_____

The child was born: ☐Vaginally ☐By C-section
If by C-section, why: _____

Birth Hospital: _____

Birth location:

Country: _____
City: _____
State (if applicable): _____

Birth weight: ☐☐.☐☐ kg
Birth Length: ☐☐☐ . ☐☐cm
Birth head circumference: ☐☐☐ . ☐☐cm

Did your child have any problems after delivery or require admission to the Neonatal Intensive Care Unit (NICU)? ☐Yes ☐No

If yes, please explain:
_____
_____

Did he/she pass the:
Newborn metabolic screen: ☐Yes ☐No ☐Unsure
Newborn hearing screen: ☐Yes ☐No ☐Unsure

How many days old was child when he/she went home from the hospital? ☐☐

Did the child have any other problems in the first few days of life? ☐Yes ☐No
If yes, please explain: _____
_____

APPENDIX 4 – MEDICAL QUESTIONNAIRE FOR MALE SIBLINGS OF STUDY SUBJECTS

Medical Questionnaire for Male Siblings of Study Subjects

*One questionnaire to be completed by each male sibling

Participant's Initials: ☐☐☐

Participant's ID #: ☐☐☐
*To be completed by study personnel

Gender: ☐Male

Today's Date: ☐☐/☐☐/☐☐☐☐

Date of birth: ☐☐/☐☐/☐☐☐☐
DD/MM/YYYY

Are you currently experiencing any major medical problems that would prevent you from participating in this study? ☐Yes ☐No

Do you have a known hypersensitivity to pilocarpine or pilocarpine-like muscarinic agonists (Examples: Urecholine, Salagen, Pilocar, and Provocholine)? ☐Yes ☐No

Do you have a pacemaker? ☐Yes ☐No

Have you been diagnosed with HED? ☐Yes ☐No

If yes, age at diagnosis: ☐0-5 years ☐6-17 years ☐≥18 years

Do you have any family members diagnosed with HED? ☐Yes ☐No

If yes, check all that apply:
☐Mother
☐Father
☐Sisters
☐Brothers
☐Aunts
☐Uncles
☐Other
If other, specify:

Have you or any family member(s) had genetic testing for HED? ☐Yes ☐No

Do you know the genetic test results? ☐Yes ☐No

Have you ever been referred to any of the following types of physicians?

Dermatologist	☐Yes	☐No
Pediatric dermatologist	☐Yes	☐No
Geneticist	☐Yes	☐No
Genetic counselor	☐Yes	☐No
Dentist	☐Yes	☐No
Pediatric dentist	☐Yes	☐No

Do you have decreased sweating?	☐Yes ☐No
Do you sweat on certain parts of your body?	☐Yes ☐No
If so, from what body part(s) do you sweat and at what age did you notice you started sweating in that area?	
Body Part: ____________ Age you noticed:	☐0-5 yrs ☐11-17 yrs ☐6-10 yrs ☐≥18 yrs
Body Part: ____________ Age you noticed:	☐0-5 yrs ☐11-17 yrs ☐6-10 yrs ☐≥18 yrs
Body Part: ____________ Age you noticed:	☐0-5 yrs ☐11-17 yrs ☐6-10 yrs ☐≥18 yrs
Body Part: ____________ Age you noticed:	☐0-5 yrs ☐11-17 yrs ☐6-10 yrs ☐≥18 yrs
Body Part: ____________ Age you noticed:	☐0-5 yrs ☐11-17 yrs ☐6-10 yrs ☐≥18 yrs
Body Part: ____________ Age you noticed:	☐0-5 yrs ☐11-17 yrs ☐6-10 yrs ☐≥18 yrs
Do you have unexplained fevers?	☐Yes ☐No
Did you ever suffer from seizures associated with fever?	☐Yes ☐No
Do you suffer from heat intolerance?	☐Yes ☐No
Is your exercising limited by heat intolerance?	☐Yes ☐No

Does your decreased sweating/heat intolerance affect your: **Check all that apply*	☐Daily life ☐Choice of occupation ☐Involvement in indoor sports ☐Involvement in outdoor sports ☐Decision to live in cooler climate ☐Choice of vacation destinations ☐Ability to travel

Have you experienced hair or eyebrow thinning or scalp hair loss?	☐Yes ☐No
If yes, what age were you when you noticed the loss of hair?	☐0-5 yrs ☐6-10 yrs ☐11-17 yrs ☐≥18 yrs
How often do you get your hair cut?	☐Daily ☐Weekly ☐ Monthly ☐Yearly
Do you get haircuts less often than unaffected siblings/ classmates?	☐ Yes ☐ No
Have you ever tried a topical treatment to reduce hair thinning?	☐Yes ☐No

Do you have problems with your teeth (no teeth, missing or misshapen teeth)?			☐Yes ☐No
If yes, describe age of treatment with dentures and/or implants if applicable (check all that apply):		Dentures	Implants
	1-5 years	☐	☐
	6-10 years	☐	☐
	11-17 years	☐	☐
	≥18 years	☐	☐
To the best of your knowledge how many baby teeth did you develop?			☐☐
To the best of your knowledge how many adult teeth did you develop?			☐☐
Do you suffer from dry mouth?			☐Yes ☐No
Do you suffer from dry eyes?			☐Yes ☐No
Do you require eye drops on a regular basis?			☐Yes ☐No
Do you suffer from frequent eye infections?			☐Yes ☐No

Did you have chronic nasal drainage/blockage as a child?		☐Yes ☐No
Did you suffer from nosebleeds as a child?		☐Yes ☐No
If yes, at what age did you first notice them?	☐0-5 yrs ☐6-10 yrs	☐11-17 yrs ☐≥18 yrs
Do you still experience nosebleeds?		☐Yes ☐No
How many times per year do you have nosebleeds?	☐☐	
Did you have respiratory related problems as a child?		☐Yes ☐No
If yes, were you ever hospitalized for antibiotic therapy?		☐Yes ☐No
Do you suffer from sinus infections most years?		☐Yes ☐No
If so, at what age did these sinus infections start?	☐0-5 yrs ☐6-10 yrs	☐11-17 yrs ☐≥18 yrs
Do you suffer from asthma?		☐Yes ☐No
If so, do you require medication to manage your asthma?		☐Yes ☐No
Do you experience a hoarseness of your voice?		☐Yes ☐No
If yes, at what age did you first notice it?		☐Yes ☐No
Is the hoarseness worse during the cold months?		☐Yes ☐No

Do you have problems with dry skin?	☐Yes ☐No
Have you ever had a diagnosis of eczema or atopic dermatitis?	☐Yes ☐No
If yes, have you tried prescription medications?	☐Yes ☐No

If yes, list medications:

Do you have a family history of eczema (other than XLHED males)? ☐Yes ☐No

Hypohidrosis Severity 5-Point Likert Scale

1	2	3	4	5
Sweat as much as people without ED	Sweat a little less than people without ED (no problems in hot weather)	Some problems in sweating (sometimes have problems in hot weather)	A little sweating (I have problems in hot weather	No sweating at all (I have problems in hot weather)

Alopecia (hair loss or thinning) Severity 5-Point Likert Scale

1	2	3	4	5
Normal hair	Mild (<25%) hair loss	Moderate (25-75%) hair loss	Severe (>75%) hair loss	No hair

APPENDIX 5 – OCULAR SURFACE DISEASE INDEX© (OSDI©)

Provided as a separate document.

REFERENCES

Black, MM, Matula K. 2000. *Essentials of Bayley Scales of Infant Development-II Assessment*. New York, J Wiley & Sons, Inc.

Blüschke G, Nusken KD, Schneider H. 2010. Prevalence and prevention of severe complications of hypohidrotic ectodermal dysplasia in infancy. *Am J Med Gen A*. 86: 397-9.

Casal M, Lewis J, Mauldin E, Tardivel A, Ingold K, Favre M, Paradies F, Demotz S, Gaide O, Schneider P. 2007. Significant Correction of Disease after Postnatal Administration of Recombinant Ectodysplasin A in Canine X-Linked Ectodermal Dysplasia. *Am J Hum Genet*. 81: 1050-1056.

Chawla, D, Agarwal R, Deorari A, Paul, V. 2008. Fluid and electrolyte management in term and preterm neonates. NICU Protocol. Division of Neonatology, Department of Pediatrics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi.

Clarke A, Sarfarazi M, Thomas NS, Roberts K, Harper PS. 1987. X-linked hypohidrotic ectodermal dysplasia: DNA probe linkage analysis and gene localization. *Hum Genet.* 75(4): 378-80.

Cloherty JP, Eichenwald EC, Stark AR. 2004. Manual of Neonatal Care (Fifth Ed). Philadelphia, PA: Lippincott, Williams & Wilkins.

Cluzeau C, Hadj-Rabia S, Bal E, Clauss F, Munnich A, Bodemer C, Headon D, Smahi A. 2012. The EDAR370A allele attenuates the severity of hypohidrotic ectodermal dysplasia caused by EDA gene mutation. *Br J Dermatol* 166:678-81.

Dietz J, Kaercher T, Schneider AT, Zimmerman T, Huttner K, Johnson R, Schneider H. 2013 Apr 4. Early respiratory and ocular involvement in X-linked hypohidrotic ectodermal dysplasia. *Eur J Pediatr* Epub ahead of print.

Ectodysplasin A (Fc:EDA1 aka EDI200) Replacement Therapy In A Canine Model Of Ectodermal Dysplasia: Pharmacological Assessment (NCD-200-11-005). Edimer Pharmaceuticals, Inc.

EDI200: A 3-Week Intraperitoneal/Intravenous Toxicity Study in Juvenile Dogs with a 2-Week Recovery Period (1800-010). Edimer Pharmaceuticals, Inc.

EDI200: A 3-Week Intraperitoneal Toxicity Study in Juvenile Mice with a 2-Week Recovery Period (1800-009). Edimer Pharmaceuticals, Inc.

"Electronic Records: Electronic Signatures." *Code of Federal Regulations* Title 21, Pt. 11, 2011 ed.

Gaide O, Schneider P. 2003. Permanent Correction of an Inherited Ectodermal Dysplasia with Recombinant EDA. *Nat Med*. 9: 614-618.

Haycock, G. B., Schwartz, G. J., & Wisotsky, D. H. 1978. Geometric method for measuring body surface area: a height-weight formula validated in infants, children, and adults. *J Pediatr*. 93(1), 62-6.

Hey E. 1975. Thermal neutrality. *British Med Bull*. *31*(1): 69-74.

Huttner K, Grange D, Klein O, Schneider H. 2012, February. Genotype/phenotype correlations in XLHED: Insights into the biology of ectodysplasin. Poster session presented at the 2012 Dermatogenetics Conference. Miami, Florida.

Itoh H, Uebori S, Asai M, Kashiwaya T, Atoh K, Makino I. 2003. Early Detection of Orthostatic Hypotension by Quantitative Sudomotor Axon Reflex Test (QSART) in Type 2 Diabetic Patients. *Internal Med*. 42: 560-564.

Low P, Caskey P, Tuck R, Fealey R, Dyck P. 1983. Quantitative Sudomotor Axon Reflex Test in Normal and Neuropathic Subjects. *Ann Neurol*. 14: 573-580.

Mastella G, Di Cesare G, Borruso A, Menin L, Zanolla L. 2000. Reliability of sweat testing by the Macroduct collection method combined with conductivity analysis in comparison with the classic Gibson and Cooke technique. *Acta Paediatrica. 89*(8): 933-7.

Mauldin E, Gaide O, Schneider P, Casal M. 2009. Neonatal Treatment with Recombinant Ectodysplasin Prevents Respiratory Disease in Dogs with X-Linked Ectodermal Dysplasia. *Am J Med Genet A.* 149A: 2045-2049.

Miller, R. 2003. Marginal Transfer of ReoPro™ (Abciximab) Compared with Immunoglobulin G (F105), Inulin and Water in the Perfused Human Placenta In Vitro. *Placenta*. *24*(7): 727-738.

Motil KJ, Fete TJ, Fraley JK, Schultz RJ, Foy TM, Ochs U, et al. 2005. Growth Characteristics Of Children With Ectodermal Dysplasia Syndromes. *Pediatrics*. 116(2): 229-34.

Ramaswami U, Wendt S, Pintos-Morell G, Parini R, Whybra C, Leon Leal J, Santus F, Beck M. 2007. Enzyme Replacement Therapy with Agalsidase Alfa in Children with Fabry Disease. *Acta Paediatr*. 96: 122-127.

Rutter N, Hull D. 1979. Response of term babies to a warm environment. *Arch Dis Child. 54*(3): 178-183.

Seeliger F, Drögemüller C, Tegtmeier P, Baumgärtner W, Distl O, & Leeb T. 2005. Ectodysplasin-1 deficiency in a German Holstein bull associated with loss of respiratory mucous glands and chronic rhinotracheitis. *J Comp Pathol*. 132(4): 346-9.

Sjörs G, Hammarlund K, Sedin, G. 1997. Thermal balance in term and preterm newborn infants nursed in an incubator equipped with a radiant heat source. *Acta Paediatrica. 86*(4): 403-9.

Stothers J K, Warner R M. 1984. Thermal balance and sleep state in the newborn. *Early Hum Dev*. *9*(4): 313-22.

Sulyok E, Jequier E, Prod'hom L. 1976. Relationship between body size, thermal balance and thermal insulation of term infants under various ambient conditions. *Biol Neonate*. *28*: 42-56.

Sweat Duct Imaging in Mother/Newborn Dyads (ECP-005). Clinical Study Report. Edimer Pharmaceuticals, Inc.

Swischuk, L. 2003. Imaging of the Newborn, Infant and Young Child (Fifth). Philadelphia, PA: Lippincott, Williams and Wilkins.

The Effect of Ectodysplasin A (Fc: EDA1) Replacement Therapy in a Canine Model of Ectodermal Dysplasia (NCD-22-11-004). Edimer Pharmaceuticals, Inc.

Ulm M R, Kratochwil A, Ulm B, Solar P, Aro G, Bernaschek, G. 1998. Three-dimensional ultrasound evaluation of fetal tooth germs. *Ultrasound Obst Gyn*. *12*(4): 240-3.

Zankl A, Addor M, Cousin P, Gaide A, Gudinchet F, Schorderet D. 2001. Fatal outcome in a female monozygotic twin with X-linked hypohidrotic ectodermal dysplasia (XLHED) due to a de novo t(X;9) translocation with probable disruption of the EDA gene. *Eur J Pediatr*. 160: 296-99.

Protocol Version 6
11 Feb 2015

Clinical Protocol

A Phase 2 open-label, dose-escalation study to evaluate the safety, pharmacokinetics, immunogenicity and pharmacodynamics/efficacy of EDI200, an EDA-A1 replacement protein, administered to male infants with X-Linked Hypohidrotic Ectodermal Dysplasia (XLHED)

Protocol: ECP-002

Investigational Product: EDI200

Sponsor:

Edimer Pharmaceuticals, Inc.
55 Cambridge Parkway
Suite 102W
Cambridge MA 02142

IND Number: 109262
EudraCT Number: 2012-003561-17

Issue Date: 11FEB2015
Version: 6

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11FEB2015, version 6.1***
11FEB2015, version 6.2**
*Version 2 was issued prior to the enrollment of subjects and included only minor changes for clarification
**UK only
***Germany only

Amendment #/Date	Applicable Section	Original Text	New/Revised Text/Description	Rationale
6 11FEB2015	Executive Summary	Minor changes made to reflect change in dose for third cohort from 30 mg/kg to 20 mg/kg	N/A	DSMB recommendation
6 11FEB2015	Synopsis	Minor changes made to reflect change in dose for third cohort from 30 mg/kg to 20 mg/kg	N/A	DSMB recommendation
6 11FEB2015	1.1	Minor changes made to reflect change in dose for third cohort from 30 mg/kg to 20 mg/kg	N/A	DSMB recommendation
6 11FEB2015	3.1.2	Minor changes made to reflect change in dose for third cohort from 30 mg/kg to 20 mg/kg	N/A	DSMB recommendation
6 11FEB2015	3.1.5	Minor changes made to reflect change in dose for third cohort from 30 mg/kg to 20 mg/kg	N/A	DSMB recommendation
6 11FEB2015	3.3.8	Minor changes made to reflect change in dose for third cohort from 30 mg/kg to 20 mg/kg	N/A	DSMB recommendation
6 11FEB2015	4.8	Minor changes made to reflect change in dose for third cohort from 30 mg/kg to 20 mg/kg	N/A	DSMB recommendation
5 21NOV2014	Executive Summary	Change made to add a third cohort.	In the case that EDI200 dosing at 10 mg/kg is well tolerated with no new safety issues identified during DSMB review, that cohort 2	Dose increase to 30 mg/kg

			EDI200 exposure levels are well below those at the neonate NOAEL level, and subject sweat production is not normalized at this dose, then cohort 3 subjects will be enrolled and dosed at a ½ log increase to 30 mg/kg/dose IV, equivalent to 0.15 x the neonate NOAEL of 200 mg/kg/dose (factor of 1:6.7). And other various minor changes to reflect a third cohort and increased dose.	
5 21NOV2014	Executive Summary	Male siblings of study subjects, both affected and unaffected, will be offered enrollment in an accompanying natural history sub-study including a medical history questionnaire and a one-time, non-invasive evaluation of current clinical condition (without study drug administration, X-rays or blood draws). The results from these genetically related, untreated siblings will provide comparative data for interpreting the clinical outcomes in treated study subjects.	Male siblings of study subjects, both affected and unaffected, will be offered enrollment in an accompanying natural history sub-study including a medical history questionnaire and a one-time, non-invasive evaluation of current clinical condition (without study drug administration, skin biopsy samples, X-rays or blood draws). The results from these genetically related, untreated siblings will provide comparative data for interpreting the clinical outcomes in treated study subjects.	Clarification
5 21NOV2014	Synopsis	N/A	Minor changes to reflect a third cohort and increased dose	Dose increase to 30 mg/kg
5 21NOV2014	Time and Events Schedule	N/A	Minor changes made to remove sweat duct density assessment and eye exam from the month 2 visit.	Data from the first four subjects does not support conducing these procedures at month 2.
5 21NOV2014	1.1	Change made to add a third cohort.	In the case that EDI200 dosing at 10 mg/kg is well tolerated with no new safety issues identified during DSMB review, that cohort 2 EDI200 exposure levels are	Dose increase to 30 mg/kg

			well below those at the neonate NOAEL level, and subject sweat production is not normalized at this dose, then cohort 3 subjects will be enrolled and dosed at a ½ log increase to 30 mg/kg/dose IV, equivalent to 0.15 x the neonate NOAEL of 200 mg/kg/dose (factor of 1:6.7).	
5 21NOV2014		Cohort enrollment - The Phase 2 neonate XLHED study is designed to enroll two cohorts of at least 3 subjects each (cohort size determined by rate of enrollment and sponsor discretion), consistent with the practical aspects of study enrollment in ultra-rare orphan disorders and the unique challenge of enrolling newborns. Enrollment and dosing of all subjects in neonate cohort 1 (3 mg/kg/dose) will be completed and reviewed prior to initiating dosing of subjects in neonate cohort 2 (10 mg/kg/dose).	Cohort enrollment - The Phase 2 neonate XLHED study is designed to enroll up to three cohorts of at least 3 subjects each (cohort size determined by rate of enrollment and sponsor discretion), consistent with the practical aspects of study enrollment in ultra-rare orphan disorders and the unique challenge of enrolling newborns. Enrollment and dosing of all subjects in neonate cohort 1 (3 mg/kg/dose) will be completed and reviewed prior to initiating dosing of subjects in neonate cohort 2 (10 mg/kg/dose). Similarly, enrollment and dosing of subjects in neonate cohort 2 will be completed and reviewed prior to enrollment and dosing of cohort 3 subjects (30 mg/kg/dose).	Dose increase to 30 mg/kg
5 21NOV2014	3.1.1	N/A	Various minor changes made regarding a third cohort.	Dose increase to 30 mg/kg
5 21NOV2014	3.1.2	Change made to add a third cohort.	Recognizing that translation from animal results and PK modeling to human study results may be imperfect, especially in the dose parameters, the protocol includes an option for enrolling a third cohort at a ½ log increase in dosing to 30 mg/kg/dose, again 5 doses over 15 days. It is	Dose increase to 30 mg/kg

			anticipated that the criteria for initiating cohort 3 enrollment will include safety review of cohort 2 data by the DSMB including PK analysis, and a less than maximal clinical response in the cohort 2 subjects.	
5 21NOV2014	3.1.5	N/A	Various minor changes made regarding a third cohort.	Dose increase to 30 mg/kg
5 21NOV2014	3.3	6-10	9-15	Dose increase to 30 mg/kg
5 21NOV2014	3.3.8	N/A	Various minor changes made regarding a third cohort.	Dose increase to 30 mg/kg
5 21NOV2014	4.8	Change made to add a third cohort.	• After dosing is completed in XLHED cohort 2, the Sponsor may elect to enroll a third cohort with EDI200 dosing at 30 mg/kg/dose. Prior to initiating dosing of this third cohort, the DSMB will review safety and PK data from cohorts 1 and 2 in order to provide guidance on advancing to dosing at the higher level.	Dose increase to 30 mg/kg
5 21NOV2014	5.4	Changes made to remove sweat duct density assessment and dry eye exam from the 2 month visit.	N/A	Data from the first four subjects does not support conducing these procedures at month 2.
5 21NOV2014	6.1	10 subjects	15 subjects	Dose increase to 30 mg/kg
5 21NOV2014	6.4	Changes made to remove sweat duct density assessment and dry eye exam from the 2 month visit.	N/A	Data from the first four subjects does not support conducing these procedures at month 2.

3 12JUN2013	Cover Page, Synopsis	A Phase 2 open-label, dose-escalation study to evaluate the safety, pharmacokinetics and pharmacodynamics/efficacy of EDI200, an EDA-A1 replacement protein, administered to male infants with X-Linked Hypohidrotic Ectodermal Dysplasia (XLHED)	A Phase 2 open-label, dose-escalation study to evaluate the safety, pharmacokinetics, immunogenicity and pharmacodynamics/efficacy of EDI200, an EDA-A1 replacement protein, administered to male infants with X-Linked Hypohidrotic Ectodermal Dysplasia (XLHED)	Immunogenicity added to study title
3 12JUN2013	Executive Summary	See 02APR2013 protocol version 2	Several minor changes made to Executive Summary	Clarification
3 12JUN2013	Time and Events Schedule	Change made to biopsy and PK sample schedule	Biopsy removed from Month 6 visit, PK sample removed from Day 15 visit	Correction and clarification
3 12JUN2013	Time and Events Schedule	Change made to PK sample schedule	PK sample added to baseline and month 6	Modification of PK sample schedule (similar minor changes made throughout protocol)
3 12JUN2013	Time and Events Schedule	Change made to safety labs and immunogenicity sample schedule	Safety labs and immunogenicity sample moved from day 15 to day 16	Modification of safety labs and immunogenicity sample schedule (similar minor changes made throughout protocol)
3 12JUN2013	Time and Events Schedule	A full physical exam will be conducted at baseline, treatment days 7 and 14 and at the months 2, 4 and 6 follow-up visits. The full physical exam will include weight, height, head circumference and vital signs. A brief physical exam will be conducted at treatment days 0, 1, 4, 11, 15 and 21. The brief physical exam will include vital signs. On dosing days vital signs will also be collected every 4 hours following the end of the infusion for 24 hours.	A full physical examination will be conducted at baseline, day 21, months 2, 4, and 6. With the full physical examination will be the following quantitative assessments; weight, height, head circumference and vital signs (temperature, blood pressure, heart rate and respiratory rate). A brief physical examination will be conducted at treatment days 0, 1, 4, 7, 11, 14 and 15. The brief physical examination will include overall appearance (normal or abnormal and if abnormal why), skin appearance, cardiovascular, pulmonary	Clarification on components of brief and full physical exam

			and abdominal evaluation. With the brief physical examination will be weight and a set of vital signs (temperature, blood pressure, heart rate and respiratory rate). On dosing days vital signs will also be collected pre- and post dosing as described in section 3.3.8.	
3 12JUN2013	Time and Events Schedule, 4.5.2	New text added	Time windows added for acceptable sampling	Provision for obtaining samples outside of specified time points
3 12JUN2013	Time and Events Schedule	Subjects may provide dental X-rays from an outside source. No dental radiographs will be obtained at the study site.	No dental radiographs will be taken as part of this sibling sub-study. Subjects will be asked to provide copies of recent dental X-rays from an outside source.	Clarification that no dental radiographs are done as part of the sibling sub-study (similar minor changes made throughout protocol)
3 12JUN2013	Time and Events Schedule	See 02APR2013, protocol version 2	Several minor changes made to Time and Events Schedule	Clarification
3 12JUN2013	1.1	See 02APR2013, protocol version 2	Several minor changes made	Clarification
3 12JUN2013	3	See 02APR2013, protocol version 2	Several minor changes made	Clarification
3 12JUN2013	3.1.5	The schedule of events for the In-Clinical portion of the study is presented in the Time and Events Table. In each cohort the first subject enrolled will complete dosing of study medication, and if no significant AEs are observed then the remaining cohort subjects may begin dosing one week later. Subjects will have vital sign monitoring during and for 24 hours following each dose of study drug. The Medical Monitor and study PI will be responsible for evaluation of all AE and safety laboratory results.	The subject will be admitted to the study site during the entire dosing period. The schedule of events for this portion of the study is presented in the Time and Events Table. In each cohort, the first subject enrolled will complete the 15-day dosing period and undergo monitoring for an additional week at the study site. The site and Sponsor Medical Monitors will then review all AE and safety laboratory data. In the absence of any clinically significant AE's the remaining cohort subjects may begin dosing. It is	Clarification of dosing stratification

			anticipated that the timeframe from last dose of the first cohort subject through AE review will be approximately 2 weeks.	
3 12JUN2013	3.3.4, 3.3.6, 3.3.7	FDA	National Competent Authorities	Term FDA replaced with National Competent Authorities
3 12JUN2013	3.3.8	EDI200 will be thawed to room temperature on the day of dose administration, pooled in syringe(s) and infused via a syringe pump infusion system. The study drug shall be infused routinely over a period of 2 hours, but not to exceed 5 ml/kg/hr or 500 mg EDI200/hr.	EDI200 will be thawed to room temperature on the day of dosing, pooled in syringe(s) and administered via a syringe pump infusion system. The study drug shall be administered by slow IV infusion over at least 30 min, not to exceed 5 ml/kg/hour or 8.5 mg/min EDI200, in order to minimize the risk of infusion-related AE (refer to Investigational Brochure, Section 6.2). For more information on the preparation of EDI200 see the Pharmacy/Investigator Manual.	Clarification of infusion procedure
3 12JUN2013	3.3.8	New text added	During study drug administration and for 24 hrs following infusion the subject will have continuous heart rate and respiratory rate monitoring. A full set of vital signs including temperature, blood pressure, heart rate and respiratory rate will be documented on the following schedule: • Pre dosing - a single set of vital signs within 1 hour of initiating dose infusion • Post dosing: o 15 min after end of infusion, o 1 hr and 4 hrs after end of infusion,	Clarification of continuous monitoring (similar minor changes made throughout protocol)

			○ then q4 hrs up to 24 hrs after end of infusion If the unit in which the subject is receiving study drug requires additional monitoring, then that data will be added to the subject's record.	
3 12JUN2013	3.3.8	New text added	The intravenous site will be assessed for patency and signs of local irritation prior to the start of the infusion, every 30 minutes during infusion, and at the end of study drug infusion.	Clarification of infusion site monitoring
3 12JUN2013	4.2.1	The initial physical examination will include assessment of standard developmental milestones, and will be augmented at Months 2, 4 and 6 by the Bayley Scales of Infant Development II (BSID-II), a well-validated assessment tool for use at 1-42 months of age (Black and Matula, 2000).	The initial physical examination will include assessment of standard developmental milestones, and will be augmented at Months 2, 4 and 6 by a validated, standard of care infant assessment tool. Examples of such tools include but are not limited to the Bayley Scales of Infant Development II (BSID-II) and III (BSDI-III) and the Denver Development Screening Test II (DDST II) (Black and Matula, 2000). Whichever tool is selected should be designed for ages down to 2 months of life and should be used for all follow-up visits.	Provision for the use of other tools of development assessment
3 12JUN2013	4.3	To meet inclusion criteria for study drug administration, families of potential study subjects will be asked if their male newborn has been tested for EDA mutations that confirm the XLHED diagnosis, either prenatally or postnatally. If genetic testing has been done, verbal consent from the family will be obtained to provide documentation of test results to the study site via a secure and	To meet inclusion criteria for EDI200 administration, potential study subjects are required to have their XLHED diagnosis confirmed by genetic testing of the EDA gene and these test results relayed to the study site. EDA genetic testing itself is outside of the scope of this protocol. If requested, the families of prospective subjects in need of EDA genotyping will be referred to resources available to facilitate this testing.	Clarification of genetic testing done during screening

		confidential method including an option for electronic transmission. If not, the study site will provide a genotyping kit with an informed consent form directly to the family (no provision for fetal or amniotic fluid testing as part of this protocol). All genotyping costs will be covered by the study. It will be the responsibility of the family to have cord blood or a neonatal blood sample drawn and sent to the recommended genotyping laboratory.	Consent from the family (written or verbal) will be obtained as part of the screening process to provide the study site with documentation of genetic testing results via a secure and confidential method including an option for electronic transmission.	
3 12JUN2013	4.5.1	New text added	It will be the Principal Investigator's responsibility to assess laboratory parameters against local reference ranges and to assess the clinical significance of any out of range values.	Clarification on assessment of lab values using both CTCAE criteria and local reference ranges
3 12JUN2013	4.6.2	The PI will report all SAEs to the Sponsor in a timely fashion, <u>usually</u> within 24 hours of awareness, by completing and faxing the SAE Report Form to CTI Safety as per directions described in the Study Reference Manual.	The PI will report all SAEs to the Sponsor in a timely fashion, within 24 hours of awareness, by completing and faxing the SAE Report Form to CTI Safety as per directions described in the Study Reference Manual.	Word "usually" deleted as reporting requirements are within 24 hours
3 12JUN2013	4.8	Unscheduled DSMB reviews will take place as outlined in Section 3.3.4-3.3.7 for single or accumulated adverse events.	Unscheduled DSMB reviews will take place as outlined in Section 3.3.4-3.3.7 for single or accumulated adverse events. Additional safety-related evaluations of one or more subjects may be requested by the DSMB based on findings through the 6 month, end-of-study visit.	Provision to allow for additional DSMB-requested procedures or visits
3 12JUN2013	5.5	New text added	The Sponsor or DSMB may request unscheduled visits either during the subject's participation in the Study or after his completion. The unscheduled visits may	Provision to allow for unscheduled visits

			include additional safety-related evaluations (including blood sampling) based on findings through the 6-month, end-of-study visit.	

EXECUTIVE SUMMARY

X-linked hypohidrotic ectodermal dysplasia (XLHED) is a disorder of ectoderm development in which sweat and secretory gland hypoplasia predisposes affected infants to serious and potentially life-threatening hyperthermia and pneumonia (Clarke et al., 1987). Those XLHED patients who survive infancy face a host of ectoderm-related clinical conditions including failure to thrive, oligodontia and misshapen teeth, mid-face hypoplasia, eczema, chronic dry eyes, asthma, respiratory infections, sinusitis and chronic nosebleeds. XLHED is caused by inherited defects in the ectodysplasin gene (EDA, www.ncbi.nlm.nih.gov/omim) resulting in a deficiency of the ectoderm signaling protein EDA-A1. As is the general case with X-linked disorders, hemizygous XLHED males are more consistently and severely affected, while heterozygous XLHED females have a more variable phenotype.

In normal development, EDA-A1 acts as an ectoderm signaling molecule that binds specifically to the EDA-A1 receptor (EDAR) triggering initiation and maturation of ectoderm appendages into sweat and secretory glands, tooth buds and hair follicles. In the case of XLHED, EDA-A1 deficiency results in the absence or functional hypoplasia of the ectoderm appendages. There are no therapies currently available for XLHED that prevent or correct the underlying ectodermal abnormalities.

EDI200 is a fully humanized EDA-A1 replacement molecule under development as a novel therapeutic for XLHED. EDI200 comprises the human IgG1 Fc domain linked to the human EDA-A1 receptor-binding domain. In the course of normal ectodermal signaling, EDA-A1 monomers associate as trimers and higher order multimers that are required for activation of the EDA-A1 receptor (EDAR). The N-terminal Fc receptor portion of the EDI200 molecule serves to stabilize the intermolecular EDA-A1 associations required for EDAR binding, and to provide a potential mechanism for transplacental delivery (Miller, 2003).

On-target EDI200 activation of the EDA-A1/EDAR signaling pathway *in vivo* is evidenced by the remarkable phenotypic response in preclinical models. In XLHED-affected animals, EDI200 correction of EDA-A1 deficiency prenatally (mice) or postnatally (newborn mice and dogs) resulted in a significant and sustained improvement in the health of the treated animals (Gaide and Schneider, 2003; Casal et al., 2007; Mauldin et al., 2009). Postnatal studies in both mice and dogs demonstrated a consistent and restricted window of efficacy (Gaide and Schneider, 2003; Edimer Study NCD-11-200-005). These results support the clinical development of EDI200 as a therapeutic to be administered to XLHED-affected patients in the neonatal period or earlier.

This Phase 2 first-in-neonate study will enroll treatment-naïve, XLHED-affected male newborns for EDI200 administration initiated within the first two weeks of life. All subjects will meet entry criteria including documentation of an EDA mutation associated

with XLHED. Following Baseline evaluations, EDI200 dosing will be initiated between day-of-life (DOL) 2 and 14, with each study subject receiving 2 doses/week for a total of 5 doses. This dosing regimen mirrors that used to enhance efficacy in the dog XLHED model, considered to be most relevant to the clinical study design. Comprehensive safety, pharmacokinetic (PK), immunogenicity and pharmacodynamic (PD)/efficacy evaluations of all neonate study subjects will initiate at study enrollment and continue throughout the dosing and follow-up period (to age 6 months).

The study will enroll 9-15 subjects in up to three cohorts, with a minimum of 3 subjects per cohort. Given the challenge of identifying families where the potential study subject is yet to be born, it is expected that cohort size and time for recruitment will be variable. We anticipate enrolling subjects over a 12-24 month period. Cohort 1 study subjects will each be administered EDI200 IV at 3 mg/kg/dose x 5 doses, equivalent to 0.015 x the neonate no observed adverse effect level (NOAEL) of 200 mg/kg/dose (factor of 1:66) and well below the maximum safe starting dose in initial clinical trials as suggested by FDA guidance. This dose was associated with partial efficacy in the canine XLHED model considered most relevant to the clinical study, and was well tolerated by XLHED adults in the Phase 1 safety study (NCT01564225, www.clinicaltrials.gov)

All safety laboratory studies will be done at the individual study sites and available to the Data Safety Monitoring Board (DSMB) in real time. Following dosing of all subjects in neonate cohort 1, the DSMB will review the cohort 1 safety and PK data. If no new safety issues are identified then cohort 2 subjects will be enrolled and dosed at a ½ log increase to 10 mg/kg/dose IV, equivalent to 0.05 x the neonate NOAEL of 200 mg/kg/dose (factor of 1:20). This dose was associated with enhanced efficacy in the canine XLHED model. Prior to the dosing of XLHED neonates in cohort 2, the DSMB also will have reviewed the safety and PK data from XLHED adult cohort 2 subjects dosed at the same 10 mg/kg/dose and the same 5 dose regimen.

In the case that EDI200 dosing at 10 mg/kg is well tolerated with no new safety issues identified during DSMB review, that cohort 2 EDI200 exposure levels are well below those at the neonate NOAEL level, and subject sweat production is not normalized at this dose, then cohort 3 subjects will be enrolled and dosed at 20 mg/kg/dose IV, equivalent to 0.10 x the neonate NOAEL of 200 mg/kg/dose (factor of 1:10).

In the core study, primary outcome measures will be safety, PK and immunogenicity. Secondary outcome evaluations of pharmacodynamics (PD)/efficacy will incorporate growth and development parameters, frequency of infections and hospitalizations, facial development as monitored by computerized recognition of XLHED-associated features, and assessments of ectoderm-related physiologic functions using technologies that minimize risk to this population. From 6 months onward (end of data collection in the Phase 2 core study), the EDI200-exposed infants will be enrolled in a long-term extension study with yearly safety and age-appropriate PD/efficacy evaluations.

Male siblings of study subjects, both affected and unaffected, will be offered enrollment in an accompanying natural history sub-study including a medical history questionnaire and a one-time, non-invasive evaluation of current clinical condition (without study drug administration, skin biopsy samples, X-rays or blood draws). The results from these genetically related, untreated siblings will provide comparative data for interpreting the clinical outcomes in treated study subjects.

SYNOPSIS

Title of Study	A Phase 2 open-label, dose-escalation study to evaluate the safety, pharmacokinetics, immunogenicity and pharmacodynamics/efficacy of EDI200, an EDA-A1 replacement protein, administered to male infants with X-Linked Hypohidrotic Ectodermal Dysplasia (XLHED)
Name of Company	Edimer Pharmaceuticals, Inc.
Name of Finished Product	EDI200
Name of Active Ingredient	EDI200
Protocol Number	ECP-002
IND Number	109262
EudraCT Number	2012-003561-17
Objectives	Primary Objectives • To assess the safety, pharmacokinetics and immunogenicity of EDI200 administered to XLHED-affected neonates Secondary Pharmacodynamic/Efficacy Objectives • To assess EDI200 pharmacodynamics/ efficacy in the treatment of XLHED-affected neonates • To compare clinical and medical history data obtained from untreated male siblings to that of the XLHED-affected neonate receiving study drug
Methodology	Phase 2 open-label, three cohort, dose-escalation study
Number of Subjects	• 9-15 XLHED-affected male neonates for study drug administration • Male siblings (XLHED-affected and unaffected) as historical controls
Diagnosis and Main Criteria for Inclusion	Male neonates documented by genetic diagnosis to carry an EDA mutation associated with XLHED, and their male siblings

Test Product Dose, Route of Administration	3, 10 or 20 mg/kg/dose (IV)
Duration of Treatment	5 doses over 15 days
Pharmacodynamic/Efficacy Evaluations	• Growth and development • Infections and hospitalizations • Dentition • Facial development • Sweat gland number and function • Dry eye assessment • Thermoregulation • Skin biopsy for expression profile
Safety Evaluations	Safety laboratory blood tests, Vital Signs, Adverse Events
Pharmacokinetics Evaluations	Serial blood draws
Statistical Methods	The safety population will consist of all subjects who receive at least one dose of study medication. The PK population will consist of all subjects who receive at least one dose of study medication and have sufficient data points to obtain a plasma concentration by time profile. The PD/efficacy population will consist of all subjects who receive at least one dose of study medication and complete the follow-up assessments through at least month 2.

TIME AND EVENTS SCHEDULE – MULTI-DOSE EDI200 ADMINISTRATION

	Screening		**Baseline**	**Treatment Phase**										**Follow-up Visits**	**Study Completion**
	Prenatal[1] (Optional)	Postnatal[2] DOL 2 to DOL 12	DOL 2 to DOL 14[3]	TD 0	TD 1	TD 2	TD 4	TD 7	TD 11	TD 14	TD 15	TD 16	TD 21	Mon 2 & 4 of Life[4] (± 1 wk)	Mon 6 of Life[4] (± 2 wks)
Informed Consent	X	X	X												
Inclusion/Exclusion	X	X	X												
Genetic testing			X[5]												
Medical History	X	X[6]	X												
Safety Evaluations															
Physical Examination[7]			X	X	X		X	X	X	X	X		X	X	X
Safety Laboratory			X		X							X	X	X[8]	X
Immunogenicity			X									X		X[8]	X
Pharmacokinetic[9]			X	X	X	X				X		X	X	X[8]	X
PD/Efficacy															
Growth/Development			X											X	X
Dentition[10]			X												
Facial Development[11]			X												X
Sweat Assessments			X											X[8]	X
Dry eye Assessment			X												X
Thermoregulation[12]			X										X		
Skin biopsy sample			X		X						X				
Study Drug				X			X	X	X	X					
Adverse Events/Con Meds[13]	X														

TIME AND EVENTS SCHEDULE – MALE SIBLINGS OF STUDY SUBJECTS

	Study Enrollment	Evaluation
	From date of 1st dose study drug administered to affected sibling	Prior to Study Completion for affected sibling
Informed Consent	X	
Inclusion/Exclusion Criteria	X	
Medical History	X	
Safety Evaluations		
Physical Examination		X
Weight, Height, Vital Signs		X
XLHED-associated Outcomes		
Growth/Development		X
Infections/Hospitalizations		X
Dentition		X[14]
Facial Development		X[15]
Sweat Assessments		X
Pulmonary function[16]		X
eNO level[17]		X
Dry eye Assessment[18]		X
Adverse Events & Con Meds	X	

1. Optional prenatal screening enrollment is from end of first trimester through delivery date
2. Newborn's screening window for study inclusion is through DOL #12
3. Baseline evaluations must be completed by DOL #14
4. Follow-up visits at 2, 4 and 6 months of chronologic age
5. In the Screening process, confirmation of subject EDA genotype is required from the family. Under Baseline Events, EDAR genotyping for the phenotype-modifying polymorphism EDAR V370A will be a standard assessment (Cluzeau et al., 2012) but is not required prior to study drug administration
6. Medical history encompasses antenatal and perinatal findings including antenatal ultrasound imaging of tooth buds if performed (Ulm et al., 1998)
7. A full physical examination will be conducted at baseline, day 21, months 2, 4, and 6. With the full physical examination will be the following quantitative assessments: weight, height, head circumference and vital signs (temperature, blood pressure, heart rate and respiratory rate). A brief physical examination will be conducted at treatment days 0, 1, 4, 7, 11, 14 and 15. The brief physical examination will include overall appearance (normal or abnormal and if abnormal why), skin appearance, cardiovascular, pulmonary and abdominal evaluation. With the brief physical examination will be weight and a set of vital signs (temperature, blood pressure, heart rate and respiratory rate). On dosing days vital signs will also be collected pre- and post dosing as described in section 3.3.8.
8. Studies to be performed at 2 months but not at the 4-month visit. The 2-month evaluation will include pilocarpine-induced sweating but not confocal imaging (sweat duct density).
9. PK samples drawn pre-EDI200 dosing and post-end of infusion at approximately the following time points:

	Pre-Dose	Post-Dose							
		15 (±5) min	3 (±.5) hrs	8 (±1) hrs	18 (±2) hrs	24(±2) hrs	48 (±4) hrs	168(±8) hrs	Age 2 months (±1 wk) & 6 months (±2 wks)
D0 (dose 1)	X	X	X	X		X	X		
D14 (dose 5)	X	X	X		X		X	X	X

10. Baseline lateral jaw film only. Dental evaluation to be performed in the long-term extension study will minimize the use of dental radiographs, and allow for substitution of dental imaging obtained as part of the routine care of XLHED patients.

11. Digital analysis of non-invasive 2D facial photographs is a technology under development jointly by the Sponsor and a private company and is being explored as a tool for monitoring change in craniofacial appearance. The algorithm assesses the subject's facial structures in the neonatal period and continues through photographs taken in the extension study.
12. Thermoregulation assessment in the neonatal period is a well-documented procedure monitoring short-term temperature and vital sign response in a closed system (incubator). At an older age in the extension study, exercise-related thermoregulation will be assessed.
13. Infections/hospitalizations as PD/efficacy endpoint will be captured through adverse events
14. No dental radiographs will be taken as part of this sibling sub-study. Subjects will be asked to provide copies of recent dental X-rays from an outside source.
15. Frontal and lateral facial photographs to be taken and baby picture (age up to 1 month) to be collected if available
16. Minimum age 5 years for pulmonary testing
17. Minimum age 4 years for eNO assessment
18. A more comprehensive dry eye assessment will be performed in children as opposed to the neonates

LIST OF ABBREVIATIONS

Abbreviation	Definition
2D	Two Dimensional
ADL	Activities of Daily Living
AE	Adverse Event
AUC	Area Under the Curve
BSID	Bayley Scales of Infant Development
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTGF	Connective Tissue Growth Factor
DDST	Denver Development Screening Test
DOL	Day of Life
DSMB	Data Safety Monitoring Board
EDA	Ectodysplasin A
EDA-A1	Ectodysplasin protein A1
EDAR	Ectodysplasin-A1 Receptor
EDC	Electronic Data Capture
eCRF	Electronic Case Report Forms
eNO	Exhaled Nitric Oxide
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
I/E	Inclusion/Exclusion
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
Lgr5	Leucine-Rich G-Protein Coupled Receptor
MedDRA	Medical Dictionary for Regulatory Activities
NCD	Nonclinical Document
NCI	National Cancer Institute
NOAEL	No Adverse Effect Level
OSDI	Ocular Surface Disease Index
PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetic
RNA	Ribonucleic Acid
SAE	Serious adverse event

Shh	Sonic Hedgehog
SUSAR	Suspected Unexpected Adverse Reaction
TD	Treatment Day
XLHED	X-Linked Hypohidrotic Ectodermal Dysplasia

PI AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the conduct of the study.

PI's Signature* Date

Name of PI (Typed or Printed)

Institution Address*

Phone Number*

12FEB2015
Sponsor's Medical Monitor Signature Date

Ira Davis, MD
Name of Medical Monitor (Typed or Printed)

* If the address or phone number of the PI changes during the course of the study, written notification will be provided by the PI to the Sponsor and will not require protocol amendment(s).

1 BACKGROUND

XLHED, the most common of the ectodermal dysplasias, is caused by inherited defects in the ectodysplasin (EDA) gene that disrupt synthesis and/or function of the primary translational product EDA-A1 (www.ncbi.nlm.nih.gov/omim). In normal development, EDA-A1 acts as an ectoderm signaling molecule that binds specifically to the EDA-A1 receptor (EDAR) triggering initiation and maturation of ectoderm appendages into sweat and secretory glands, tooth buds and hair follicles. The absence of normal EDA-A1 expression results in sweat and secretory gland hypoplasia predisposing XLHED-affected infants to serious and potentially life-threatening hyperthermia and pneumonia (Clarke et al., 1987). XLHED-affected children surviving infancy face a host of life-long ectoderm-related clinical conditions including failure to thrive, oligodontia and misshapen teeth, mid-face hypoplasia, eczema, chronic dry eyes, asthma, respiratory infections, sinusitis and chronic nosebleeds. As is the general case with X-linked disorders, XLHED-affected males are more consistently and severely affected, while XLHED-affected females have a more variable phenotype.

There are no therapies currently available for XLHED that prevent or correct the underlying abnormalities of ectoderm-derived structures. In two genetically confirmed animal models of XLHED, systemic administration of recombinant EDA-A1 (EDI200) in the prenatal (mice) or postnatal (newborn mice and dogs) settings corrected many of the defects in ectoderm development resulting in a significant and sustained improvement in the health of the treated animals (Gaide and Schneider, 2003; Casal et al., 2007). To date, data in both species has demonstrated a restricted efficacy window that closes after the first several weeks of postnatal life (Gaide and Schneider, 2003; Edimer Study NCD-200-11-005). This is consistent with the well-studied timeframe for ectoderm appendage development, and supports the clinical development of EDI200 as a therapeutic to be administered to XLHED-affected patients in the newborn period or earlier.

1.1 Rationale for Study

Study Drug - EDI200 is a fully humanized EDA-A1 replacement molecule designed for parenteral administration, comprising the human IgG1 Fc sequence linked to the human EDA-A1 receptor-binding domain. The N-terminal Fc receptor portion of the EDI200 molecule serves to facilitate and stabilize the intermolecular associations required for EDAR binding, as well as providing a potential mechanism for fetal delivery (Miller, 2003). Through its unique design, EDI200 retains the EDA-A1 receptor specificity as evidenced by the targeted phenotype response in preclinical XLHED models (Gaide and Schneider, 2003; Casal et al., 2007; Mauldin et al., 2009).

Safety and PK data in Adults - Following discussions with the FDA regarding the clinical development plan for EDI200 in a pediatric indication; a Phase 1 study in XLHED-affected adults was initiated (NCT01564225, www.clinicaltrials.gov) to develop human safety and PK data in anticipation of dosing XLHED-affected neonates. Selecting XLHED-affected adults for the Phase 1 study provided a genetic and biologic relevance to XLHED-affected neonates. Enrolling adult

XLHED-affected males and females: (1) supported dosing of male XLHED neonates in the current trial; (2) provided data for the possibility of dosing XLHED-affected female neonates; and (3) initiated the collection of data necessary to support a future trial of maternal EDI200 administration. Identical dosage (mg/kg) and dosing regimens are planned for the adult and neonate XLHED studies.

Neonate Dosing Strategy: Age at Dosing Initiation; Dosing Regimen; Starting Dose

Age at Dosing Initiation – In both the mouse and dog XLHED models; early postnatal administration was associated with correction of clinically relevant abnormalities. Based primarily on the multi-dose dog data, study drug administration in this protocol is targeted to begin between day-of-life (DOL) #2 and DOL #14 (Edimer Study NCD-200-11-005).

Dose Regimen - The EDI200 dosing regimen proposed for the Phase 2 XLHED neonate study is a single course consisting of 5 doses administered at 2 doses/week. This regimen is based on results from the dog XLHED model which is most comparable to the human condition in developmental maturity at birth and in health-related endpoints (Casal et al., 2007; Edimer Study NCD-200-11-004). The 2-dose/week-regimen was incorporated into the GLP toxicology studies as well (Edimer Studies 1800-009 and 1800-010).

Starting Dose – No study-drug related adverse effects were observed at the highest EDI200 dose tested in both mouse and dog neonatal GLP toxicology studies, confirming a NOAEL of $\geq$200 mg/kg/dose (1800-009; 1800-010). Consistent with FDA guidelines for Maximum Starting Dose in Initial Clinical Trials, and incorporating a conservative approach to dosing in this vulnerable population, the first cohort of XLHED neonates will receive EDI200 at 3 mg/kg/dose IV, 0.015 x neonatal NOAEL (factor of 1/66). In the dog XLHED efficacy studies, dosing at 3 mg/kg/dose was associated with partial efficacy, which was enhanced significantly in animals receiving 10 mg/kg/dose (Edimer Study NCD-200-11-004). Safety and PK data from the Phase 1 adult study cohort treated with EDI200 at 3 mg/kg/dose x 5 doses over 15 days was reviewed by the DSMB with no reported study drug-related adverse events.

In the Phase 2 neonate study, the DSMB will review safety and PK data from neonate cohort 1, and in the absence of safety concerns, neonates will then be enrolled in cohort 2 and dosed at a pharmacologic half-log increase to EDI200 10 mg/kg/dose IV, equivalent to 0.05 x the neonatal NOAEL (factor of 1/20). Safety and PK data from the Phase 1 adult cohort 2, having received EDI200 at the same dose and the same dosing regimen, also will be reviewed by the DSMB prior to initiating dosing in neonate cohort 2. The dose for XLHED neonate cohort 2 is anticipated to maximize postnatal EDI200 efficacy based on the dog XLHED results (Edimer Study NCD-200-11-004).

In the case that EDI200 dosing at 10 mg/kg is well tolerated with no new safety issues identified during DSMB review, that cohort 2 EDI200 exposure levels are well below those at the neonate NOAEL level, and subject sweat production is not normalized at this dose, then cohort 3 subjects

will be enrolled and dosed at 20 mg/kg/dose IV, equivalent to 0.1 x the neonate NOAEL of 200 mg/kg/dose (factor of 1:10).

Cohort enrollment - The Phase 2 neonate XLHED study is designed to enroll up to three cohorts of at least 3 subjects each (cohort size determined by rate of enrollment and sponsor discretion), consistent with the practical aspects of study enrollment in ultra-rare orphan disorders and the unique challenge of enrolling newborns. Enrollment and dosing of all subjects in neonate cohort 1 (3 mg/kg/dose) will be completed and reviewed prior to initiating dosing of subjects in neonate cohort 2 (10 mg/kg/dose). Similarly, enrollment and dosing of subjects in neonate cohort 2 will be completed and reviewed prior to enrollment and dosing of cohort 3 subjects (20 mg/kg/dose).

Primary objectives - Safety labs, physical examination, vital signs, adverse events and concomitant medications, immunogenicity, and PK will be documented as outlined in the Time and Events schedule. The schedule for PK sampling, based on the preclinical and Phase 1 adult XLHED dosing results, incorporates a sparse sampling approach to limit the frequency and volumes of neonatal blood draws. The proposed PK sampling maximizes data collection for determining both the AUC and Cmax.

Pharmacodynamic/efficacy objectives - PD/efficacy endpoint assessments relevant to the biology and pathophysiology of XLHED are incorporated into the study design as outlined in the Time and Events:

- *Clinical endpoints* - growth and development (including feeding history), infections and hospitalizations (captured under adverse events).
- *Imaging assessments* - diagnostic dental radiographs (the post-treatment dental X-rays will be incorporated into the long-term extension study and hence are not described further in this protocol), antenatal ultrasound results for tooth bud development (if available as part of Obstetric care, documented in the Medical History), pre- and post-treatment facial photographs to assess changes in craniofacial features associated with XLHED and its correction.
- *Clinical biomarkers* - sweat duct number and induced sweat volume, thermoregulation and dry eye evaluation.
- *Molecular biomarkers* - skin biopsy for expression profile.

All affected and unaffected male siblings of study subjects will be offered enrollment in a natural history sub-study evaluating the medical history and clinical condition of genetically related, untreated comparators for the study subjects.

Study Duration - Total study duration for each subject receiving study drug will be approximately 6 months, including a treatment and safety/efficacy monitoring period. A long-term extension study for all subjects receiving study drug will continue safety and PD/efficacy evaluations. Study duration for male siblings in the sibling sub study will be 1-2 days.

2 OBJECTIVES

2.1 Primary Objectives

To assess the safety, pharmacokinetics and immunogenicity of EDI200 administered to XLHED-affected neonates

2.2 Pharmacodynamic/Efficacy Objectives

- To assess the pharmacodynamics/efficacy of EDI200 administered to XLHED-affected neonates
- To compare clinical data and medical history obtained from untreated male siblings to that of the XLHED-affected neonates receiving study drug

3 STUDY DESIGN

3.1 Multi-Dose EDI200 Administration

3.1.1 *Brief Description and Rationale for Study Design*

X-linked hypohidrotic ectodermal dysplasia (XLHED) is a disorder of ectoderm development associated with EDA gene mutations that lead to a deficiency of the ectoderm signaling protein EDA-A1. EDI200 is a fully humanized EDA-A1 replacement molecule under development as a novel therapeutic for XLHED. In two XLHED animal models, a single course of perinatal EDI200 administration resulted in a substantial correction of abnormalities in ectoderm development and a significant improvement in the health of the treated animals (Gaide and Schneider, 2003; Casal et al., 2007). These preclinical findings support the clinical development of EDI200 as a therapeutic to be administered to XLHED-affected patients in the neonatal period or earlier.

The open-label Phase 2 study of EDI200 administered to XLHED-affected neonates will enroll 9-15 subjects in up to three sequential cohorts. Each study subject will have documentation of an EDA gene mutation. Cohorts will be enrolled sequentially, i.e. the first subjects will all be enrolled in cohort 1, and only after cohort 1 safety evaluation by the DSMB will subjects be enrolled in cohort 2 for dosing at a higher level. The same level of review will be applied in advancing the dosing from cohort 2 to cohort 3 subjects. Final cohort size will be determined by subject and site availability, with at least 3 subjects per cohort.

The EDI200 dose for subjects in cohort 1 is 3 mg/kg/dose, consistent with the FDA Guidelines for Maximum Safe Starting Dose in Initial Clinical Trials based on the neonate NOAEL of $\geq$200 mg/kg/dose. This dose is anticipated to be associated with partial efficacy based on the dog XLHED studies. Safety laboratory results will be available to the DSMB in real time, and a formal DSMB safety and PK review will occur following completion of dosing in cohort 1. Additionally, the DSMB will have available to it safety and PK data from all XLHED-affected adult subjects from the Phase 1 adult safety study (NCT01564225, www.clinicaltrials.gov). In the absence of a safety signal or PK concern from DSMB review, XLHED neonates in cohort 2 will be dosed at 10 mg/kg/dose, a half-log pharmacologic increase to a dose anticipated to maximize clinical benefit based on the XLHED dog studies. Cohort 3 enrollment will follow DSMB review of data from cohorts 1 and 2, including an analysis of PK parameters.

Primary outcome measures for all subjects will be safety, PK and immunogenicity. Study duration is 6 months with all subjects rolling over into a long-term extension study providing yearly evaluations. Pharmacodynamic/efficacy objectives in the Phase 2 neonate study will be limited by the timeline for ectodermal development that often exceeds 6 months, e.g. dentition. Therefore, several of these endpoints will be incorporated into the extension study protocol. There will be assessment of the following: (1) endpoints relevant to the common clinical findings in XLHED using age-appropriate technologies, e.g. growth and development, infections and hospitalizations, sweat duct counts and stimulated sweat production, pre-treatment dentition,

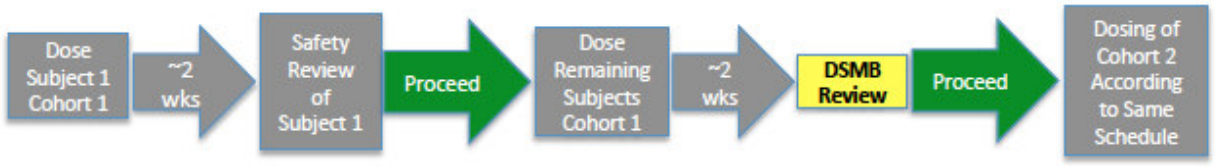
and thermoregulation; (2) change from baseline in craniofacial structures using a non-invasive facial recognition software program based on subject digital facial photographs (Appendix 1); and (3) change in molecular expression profile using skin biopsy samples obtained pre- and post-study drug exposure.

3.1.2 *Starting and Target Dose/Dosing Regimen*

The proposed starting dose is consistent with the FDA Guidelines for Maximum Safe Starting Dose in Initial Clinical Trials, based on the neonate GLP toxicology studies in two species that demonstrated a NOAEL of ≥200 mg/kg (MPI Study 1800-009 and 1800-010). Cohort 1 subjects will be dosed with EDI200 at 3 mg/kg/dose IV, 0.015 x neonate NOAEL (factor of 1/66). The proposed dosing regimen of 2 doses/week x 5 doses, beginning within the first 2 weeks of life, is supported by the dosing regimen in the GLP toxicology studies. This dose and dosing regimen is in the range of anticipated partial efficacy in the dog XLHED model, considered the most relevant species for endpoint assessment.

Prior to enrolling subjects in neonate cohort 1, the DSMB reviewed safety and PK data from cohort 1 in the Phase 1 XLHED study (NCT01564225) where adult XLHED subjects were administered EDI200 at the same dose (3 mg/kg/dose) and dosing regimen (5 doses total at 2 doses/week). No study drug-related adverse events were reported. In neonate cohort 1, the first subject enrolled will complete dosing followed by a ~2-week safety review. If no safety concerns are observed, the remaining cohort 1 subjects will begin dosing. Dosing for individual subjects will be on a mg/kg basis.

Once all subjects in neonate cohort 1 have received their IV dosing, the DSMB will review safety and PK data. In the absence of safety concerns following DSMB review of cohort 1 data, neonates in cohort 2 will be dosed at a pharmacologic half-log increase to 10 mg/kg/dose, 0.05 x neonate NOAEL (factor of 1/20), following the same 5-dose regimen (see figure below). The dose and dosing regimen for neonate cohort 2 is in the range anticipated to maximize postnatal efficacy based on results from the dog XLHED model. Dosing of subjects in cohort 2 is sequential as described in cohort 1. Subject enrollment and cohort initiation will be according to the following schedule:

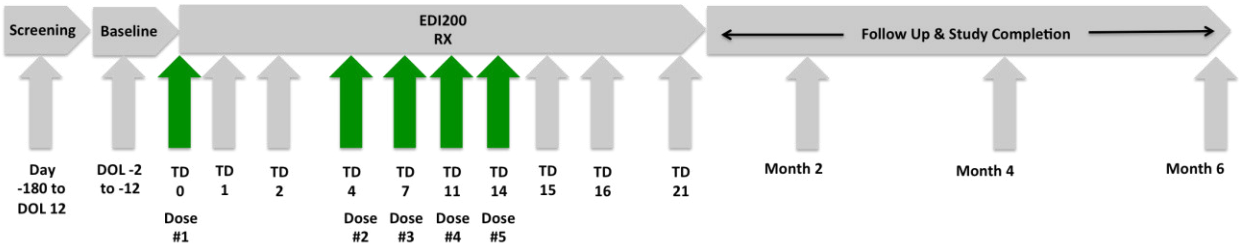


*The above schedule is repeated in cohort 2 to proceed to cohort 3

Recognizing that translation from animal results and PK modeling to human study results may be imperfect, especially in the dose parameters, the protocol includes an option for enrolling a third cohort at 20 mg/kg/dose, again 5 doses over 15 days. It is anticipated that the criteria for

initiating cohort 3 enrollment will include safety review of cohort 2 data by the DSMB including PK analysis, and a less than maximal clinical response in the cohort 2 subjects. The study will be conducted in age-appropriate clinical facilities by medical staff with appropriate levels of training and expertise and an understanding of the investigational medicinal product, its target and mechanism of action. There will be immediate access to facilities for the treatment of medical emergencies including an Intensive Care Unit.

The study timeline and visit dates for each subject are as follows:



3.1.3 *Screening*

A family with a male fetus/newborn with a clinical suspicion of XLHED may inquire to receive study information by phone, email or directly at a study site (also available on www.clinicaltrials.gov). If the family then wishes to be considered for study participation, they have the following options:

1. Prenatal Screening Enrollment (optional): the family of a male fetus at risk for XLHED may provide Informed Consent (ICF1) for data collection to begin in order to evaluate eligibility for newborn EDI200 treatment (see Sections 3.3.1 and 3.3.2). Entering the screening process early will allow for discussion and planning to minimize the potential family disruption that is likely to accompany early postnatal transfer to the study site if the subject is to be enrolled in the treatment protocol. The language of ICF1 will state clearly that once all Inclusion/Exclusion (I/E) criteria are met, an additional Informed Consent (ICF2), obtained postnatally, will be required in order to enroll the XLHED-affected neonate into the treatment portion of the study. The enrollment window for treatment encompasses the period from DOL #2 through DOL #12 (allowing a minimum of two days for transfer to the study site and baseline assessments prior to DOL #14, the last day study drug dosing can be initiated).

2. Postnatal Screening Enrollment: in the absence of Prenatal Screening Enrollment, the family of a male newborn at risk for XLHED may provide Informed Consent (ICF1) for data collection to begin in order to evaluate eligibility for the newborn EDI200 treatment (see Sections 3.3.1 and 3.3.2). The language of ICF1 will state clearly that once all Inclusion/Exclusion (I/E) criteria are met, an additional Informed Consent (ICF2) will be required in order to enroll the XLHED-affected neonate into the treatment portion of the study. The enrollment window for treatment encompasses the period from DOL #2 through DOL #12 (allowing a minimum of two days for

transfer to the study site and baseline assessments prior to DOL #14, the last day study drug dosing can be initiated).

A key inclusion criterion for the treatment protocol is verification of the XLHED diagnosis through EDA mutation testing. As part of the screening process, genetic testing results may be provided by the family to the study site via a secure and confidential method including the option for electronic transmission. If genotyping confirmation is not available at the time of Screening Informed Consent, the families of prospective subjects will be referred to resources available to facilitate rapid genotype testing at an accredited laboratory.

Families may be considering delivery at a clinical study site to facilitate treatment of their XLHED-affected son as soon as possible after birth. Any such decision is outside of this protocol and would be a private matter between the family, their health care providers, their insurance company, and the delivery service at the study site. Delivery at the study site would not commit the family to have their newborn participate in the treatment protocol, nor would it commit the PI and study site to enroll the XLHED-affected male neonate unless and until he met all the required I/E criteria and a treatment Informed Consent (ICF2) was signed by both parents (if reasonably available).

If the XLHED-affected neonate meeting inclusion/exclusion criteria is not born at the study site, the study team will assist in and cover all reasonable expenses associated with his transfer to the site. If medical transport is required, this will occur under specific Informed Consent (ICF-T) requiring signatures of both parents (if reasonably available). The window for transfer to the study site must allow for the neonate to complete Baseline evaluations in a timely manner prior to DOL #14.

3.1.4 *Baseline*

Baseline evaluation will begin with confirmation of treatment inclusion/exclusion criteria and documentation of relevant family, pregnancy and neonatal medical history. Baseline assessments of the XLHED-affected male infant as described below are to be completed prior to first dose study drug. To date, there is little data published describing evaluation techniques for XLHED patient in the newborn period. The Sponsor has experience with using the novel, minimally invasive technologies that are incorporated into this study protocol (www.edimerpharma.com/Publications and News/Publications and Abstracts)

In this Phase 2 protocol, baseline assessments of the neonate study subjects will serve three purposes. First, they will verify the general health of the XLHED-affected infant including documentation of developmental status and full physical examination. Second, blood samples will be collected for pre-treatment safety laboratory values, documentation of the absence of EDI200 and anti-EDI200 antibodies, and genotyping of the EDAR V370A polymorphism that has the potential to modify the XLHED-phenotype. Third, they will document pre-treatment ectoderm status related to EDA-A1 deficiency, including sweat duct number, induced sweat

volume, presence/absence of dentition on lateral jaw radiograph, dry eyes, digital 2D facial photograph for XLHED facial appearance, thermoregulation imbalance and skin biopsy for expression profile.

3.1.5 *Treatment Period*

The subject will be admitted to the study site during the entire dosing period. The schedule of events for this portion of the study is presented in the Time and Events Table. In each cohort, the first subject enrolled will complete the 15-day dosing period and undergo monitoring for an additional week at the study site. The site and Sponsor Medical Monitors will then review all AE and safety laboratory data. In the absence of any clinically significant AE's the remaining cohort subjects may begin dosing. It is anticipated that the timeframe from last dose of the first cohort subject through AE review will be approximately 2 weeks.

Each subject will be administered 5 doses of EDI200, administered IV on Treatment Days (TD) 0, 4, 7, 11 and 14, with vital sign monitoring during and for 24 hours following each dose of study drug. The Treatment Day for doses two through five may be $\pm$1 day, but doses must be at least 48 hours apart. Subjects in cohort 1 will be dosed at 3 mg/kg/dose calculated on Baseline weight.

On TD 0, subjects will have the following evaluations performed prior to dosing: brief physical exam, AE and concomitant medication assessment. Subjects will be administered dose 1 of study drug with vital sign monitoring during and for 24 hrs post-dose. Full details of the vital sign monitoring plan are described in Section 3.3.8. Sparse PK sampling time points post-dosing are described in Section 4.5.2.

On TD 1, subjects will have the following evaluations performed: brief physical exam, AE and concomitant medication assessment, safety laboratories, PK sampling and skin biopsy for expression profile (both approximately 24-hour post dose 1).

On TD 2, subjects will have the following evaluations performed: AE and concomitant medication assessment and PK sampling (approximately 48-hour post dose 1).

On TD 4, subjects will have the following evaluations performed prior to dosing: brief physical exam, AE and concomitant medication assessment. Subjects will be administered dose 2 of study drug with vital sign monitoring during and for 24 hrs post-dose.

On TD 7, subjects will have the following evaluations performed prior to dosing: brief physical exam and AE and concomitant medication assessment. Subjects will be administered dose 3 of study drug with vital sign monitoring during and for 24 hrs post-dose.

On TD 11, subjects will have the following evaluations performed prior to dosing: brief physical exam and AE and concomitant medication assessment. Subjects will be administered dose 4 of study drug with vital sign monitoring during and for 24 hrs post-dose.

On TD 14, subjects will have the following evaluations performed prior to dosing: brief physical exam and AE and concomitant medication assessment, and PK sampling. Subjects will be administered dose 5 of study drug with vital sign monitoring during and for 24 hrs post-dose. Sparse PK sampling time points post-dosing are described in Section 4.5.2.

On TD 15, subjects will have the following evaluations performed: brief physical exam, AE and concomitant medication assessment, and a skin biopsy obtained approximately 24 hours after administration of the last dose of study drug.

On TD 16, subjects will have the following evaluations performed: AE and concomitant medication assessment, safety laboratories, immunogenicity sampling, and PK sampling (approximately 48-hour post dose 5).

On TD 21, subjects will have the following evaluations performed: full physical examination, AE and concomitant medication assessment, post-treatment thermoregulation assessment, safety laboratories and PK sampling (approximately 168-hour post dose 5).

The remainder of the study procedures through Month 6 are described in the post-treatment section, Section 3.1.6.

Dose escalation in XLHED neonate cohorts will not occur until a review of safety and PK data from prior XLHED neonate cohorts has been completed by the DSMB, approximately three weeks after the last subject is dosed in each previous cohort. Assuming no safety or PK concerns following DSMB review, subjects in XLHED neonate cohort 2 will be dosed with EDI200 at 10 mg/kg/dose IV, a pharmacologic half-log increase. Subjects in XLHED neonate cohort 3 will be dosed with EDI200 at 20 mg/kg/dose IV. As part of the safety-monitoring program, prior to dosing subjects in each neonate cohort the DSMB will have reviewed safety and PK data from adults in the Phase 1 adult XLHED study where subjects received EDI200 at 3 and 10 mg/kg/dose in a similar dosing regimen (5 doses total at 2 doses/week).

3.1.6 *Post-Treatment Follow Up*

The post-treatment visits at Months of Life 2, 4 and 6 are designed to capture safety, immunogenicity and PD/efficacy data at appropriate timepoints following study drug exposure. In addition, PK data will be collected at Months of Life 2 and 6 visits. The post-treatment frequency of visits to the study site represents a balance between the acquisition of informative data and minimizing the travel stresses for the infant subject and his family. These evaluations will not supplant the subject's normal well-child care visits and immunizations by his primary care provider.

At Month 2 of life, subjects will have the following evaluations: full physical exam, AE and concomitant medication assessment, safety laboratories, PK and immunogenicity sampling, and PD/efficacy evaluations including growth and development and induced sweating. Expected stay at the study site location (i.e. within the vicinity of the study site) is 1-2 days.

At Month 4 of life, subjects will have the following evaluations: full physical exam, AE and concomitant medication assessment, and PD/efficacy evaluations including growth and development. Expected stay at the study site location (i.e. within the vicinity of the study site) is 1-2 days.

At Month 6 of life, subjects will have the following evaluations: full physical exam, AE and concomitant medication assessment, safety laboratories, PK and immunogenicity sampling, and PD/efficacy evaluations including growth and development, induced sweating and sweat duct imaging, dry eye assessment and digital facial photographs. Expected stay at the study site location (i.e. within the vicinity of the study site) is 1-2 days.

The conclusion of the core study is defined as the last visit of the last participant.

3.2 XLHED-Affected and Unaffected Male Siblings of Study Subjects

All male siblings (including multiple male siblings of a single neonate) of enrolled XLHED-affected neonates will be offered the opportunity to participate in a non-treatment, non-invasive evaluation providing historical control data for this open-label study. The technologies involved will be modeled on the core study evaluations, with the exception that no X-rays will be taken; no blood draws and no tissue sampling will be involved. The evaluations will take place at the study site and will include Informed Consent and Assent, if applicable, medical history, physical examination, vital signs including weight and height, digital facial photographs (frontal and lateral), growth and development assessments, induced sweating and sweat duct imaging, pulmonary function testing and eNO levels when age-appropriate (see Time & Events Schedule), dry eye evaluation and dental examination. Siblings will be asked to provide copies of their most recent dental radiographs. Expected stay at the study site location (i.e. within the vicinity of the study site) is 1-2 days.

3.3 Study Subjects

This Phase 2 study will enroll 9-15 XLHED-affected male neonates for study drug administration, and includes the optional enrollment of all male siblings, both affected and unaffected, for non-invasive evaluations.

3.3.1 *Inclusion Criteria*

Subjects for study drug administration must meet all of the following criteria to be enrolled:

1. Male with genetic confirmation of an XLHED diagnosis.
2. Subject must be at least 48 hours age and no older than 14 days.
3. Subject will have reached term (defined as 37 weeks gestation or older) prior to receiving first dose study drug.
4. Written informed consent of both parents (if reasonably available) must be obtained for treatment of their XLHED-affected male infant.
5. Neither mother nor the XLHED-affected male infant known to have received an investigational study drug in the 9 months prior to study subject enrollment in this study.
6. No major medical issues that the PI considers a contraindication to participation.

Male siblings of subjects receiving study drug must meet all of the following criteria to be enrolled in the natural history sub-study (no age limit involved):

1. Provide written informed consent/assent.
2. A full or half-sibling of a study subject where the study subject has received at least one dose of study drug in the Phase 2 XLHED Neonate Study and has not yet completed the study.
3. No major medical issues that the PI considers a contraindication to participation.

3.3.2 *Exclusion Criteria*

Subjects for study drug administration who meet any of the following criteria cannot be enrolled in this study:

1. Medically significant postnatal complications or congenital anomalies outside of those considered associated with the diagnosis of XLHED.

Male siblings of subjects receiving study drug who meet any of the following criteria cannot be enrolled in the natural history sub-study:

1. Known hypersensitivity to pilocarpine or pilocarpine-like muscarinic agonists.
2. Known hypersensitivity to lidocaine or lidocaine-like agents.
3. Presence of pacemaker.
4. Subjects who are not able or are not willing to comply with the procedures of this protocol.
5. Subject has a condition, which in the opinion of the PI would not allow for safe conduct of the study.

3.3.3 *Withdrawal or Removal of Subjects from the Study*

Study subjects/guardians may elect to discontinue study subject participation and withdraw from the study at any time without prejudice. The PI or Sponsor may withdraw a subject from participation in this study for any of the following reasons:

- A protocol violation occurs,
- The subject is not compliant with study procedures,
- A serious or intolerable adverse event occurs,
- The Sponsor or PI terminates the study, or
- The subject/guardian requests to be discontinued from the study.

A discontinuation occurs when an enrolled subject ceases participation in the study prior to completion of the protocol, regardless of the circumstances. The PI will determine the primary reason for discontinuation, and it will be recorded in the case report form and in the subject's research record. A discontinuation must be reported immediately to the Sponsor if it is due to a serious adverse event. The PI will provide or arrange for appropriate follow-up for such subjects (if required), and document the course of the subject's condition. In all cases of subject discontinuation, an attempt should be made to obtain the End-of-Study evaluations at their last study visit.

3.3.4 *Subject, Cohort or Study Suspension/Termination*

The Sponsor and/or the DSMB have the right to close this study at any time for safety or administrative reasons, although this should occur only after consultation between involved parties. The IRB/IEC and all relevant local National Competent Authorities must be informed.

3.3.5 *Subject Stopping Criteria*

- All AE and safety laboratory results will be available to the Medical Monitor, PI and DSMB in real time.
- For any Grade 2 or 3 adverse event (AE) defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v4.0; Appendix 2) that is deemed possibly, probably or definitely related to study drug treatment, individual subject dosing will be held pending review and recommendations of the Medical Monitor.
- If a subject misses a single dose and then is restarted, that dose will not be made up but all subsequent doses will be administered on schedule.
- If a subject misses two consecutive doses then dosing will not be restarted, but all study follow-up visits will occur as originally scheduled.

3.3.6 *Cohort Stopping Criteria*

The study design has only one cohort being dosed with study drug at any given time. Dosing of all subjects within a cohort will be suspended for:

- Two or more individuals develop a Grade 2 or 3 AE in a similar system organ class deemed possibly, probably or definitely related to study drug treatment (CTCAE v4.0), or
- For any Grade 4 adverse event (classified as severe or life-threatening) or a serious adverse event (SAE), regardless of drug-relatedness.

In the case where cohort dosing has been suspended, DSMB review of the AEs with the Medical Monitor, study PI and Sponsor will be required prior to discussing with a subject's family the option of restarting study drug or to enrolling additional subjects in the cohort. Missed doses will not be made up. Any subject missing two consecutive doses will not be restarted on treatment, will not be considered to have completed the dosing regimen, but will have all study follow-up visits as originally scheduled. If the DSMB safety review concludes that cohort dosing may continue, an additional subject may be added to the cohort for each subject that does not complete the dosing regimen.

In the case where a DSMB safety review concludes that a cohort should not continue dosing, no additional doses will be administered to subjects in that cohort, no additional subjects will be enrolled in that cohort, and all follow-up visits for enrolled subjects will occur as originally scheduled. The Sponsor will notify both the relevant National Competent Authorities and the local IRB/IEC of the action taken. The scheduled dose escalation cohorts will be suspended, although a more conservative dose escalation strategy may be considered for a subsequent cohort, requiring DSMB, relevant National Competent Authorities and study site IRB/IEC approval.

3.3.7 *Study Stopping Criteria*

The Sponsor and/or the DSMB have the right to close this study at any time for safety or administrative reasons, with timely notification of the relevant National Competent Authorities.

Permanent halting of dosing in any cohort by the DSMB related to safety concerns will trigger an automatic review of study termination by the DSMB in communication with the Medical Monitor, study PI, and Sponsor. If it is determined that study dosing should be terminated, all follow-up visits will occur as originally scheduled for subjects having received one or more doses of study drug. Study Sponsor assumes responsibility for reporting premature study termination to all regulatory authorities and institutional review boards.

Should the study be closed prematurely, all study materials (except documentation that has to remain stored with the PI) must be returned to the Sponsor. The PI will retain all other documents until notification given by the Sponsor for destruction.

3.3.8 *Treatment*

EDI200 study drug will be provided as a sterile solution for intravenous infusion in 3 ml glass vials, approximately 2.1 ml/vial at a concentration of approximately 5 mg/ml. Vials will be labeled according to local regulations and Sponsor standards. All study drug supplies should be stored frozen at -60 °C to -90 °C.

Dosing of EDI200 will vary by cohort. Study drug administration will be as follows:

Cohort	Number of subjects	Dose	Number of Doses	Study Day of Administration
Cohort 1	3-7	3 mg/kg	5	0, 4, 7, 11, 14
Cohort 2	3-7	10 mg/kg	5	0, 4, 7, 11, 14
Cohort 3	3-7	20 mg/kg	5	0, 4, 7, 11, 14

The weight used to calculate study drug dose will be the subject's Baseline weight for all doses. If during the treatment period a subject experiences a change in weight of >10% from Baseline, the PI(s) and the Medical Monitor will review the option of adjustments to the subject's dosing.

EDI200 will be **thawed to room temperature** on the day of dosing, pooled in syringe(s) and administered via a syringe pump infusion system. The study drug shall be administered by slow IV infusion over at least 30 min, not to exceed 5 ml/kg/hour or 8.5 mg/min EDI200, in order to minimize the risk of infusion-related AE (refer to Investigational Brochure, Section 6.2). For more information on the preparation of EDI200 see the Pharmacy/Investigator Manual.

Examples are shown in the table below.

Subject Weight	EDI200 Dose (mg/kg)	Total Dose EDI200	EDI200 Conc (mg/ml)	Vol	Vol/kg	Minimum Infusion Time	ml/kg/ hr	EDI200 mg/min
3 kg	3	9 mg	5	1.8 ml	0.6 ml/kg	0.5 hrs	1.2	0.3
3 kg	10	30 mg	5	6 ml	2.0 ml/kg	0.5 hrs	4	1.0
3 kg	20	60 mg	5	12 ml	4.0 ml/kg	1 hr	4	1.0
4 kg	3	12 mg	5	2.4 ml	0.6 ml/kg	0.5 hrs	1.2	0.4
4 kg	10	40 mg	5	8 ml	2.0 ml/kg	0.5 hrs	4	1.3
4 kg	20	80 mg	5	16 ml	4.0 ml/kg	1 hr	4	1.33
5 kg	3	15 mg	5	3 ml	0.6 ml/kg	0.5 hrs	1.2	0.5
5 kg	10	50 mg	5	10 ml	2.0 ml/kg	0.5 hrs	4	1.7
5 kg	20	100 mg	5	20 ml	4.0 ml/kg	1 hr	4	1.67

During study drug administration and for 24 hrs following infusion the subject will have continuous heart rate and respiratory rate monitoring. A full set of vital signs including

temperature, blood pressure, heart rate and respiratory rate will be documented on the following schedule:

- Pre dosing - a single set of vital signs within 1 hour of initiating dose infusion
- Post dosing:
    - 15 min after end of infusion,
    - 1 hr and 4 hrs after end of infusion,
    - then q4 hrs up to 24 hrs after end of infusion

If the unit in which the subject is receiving study drug requires additional monitoring, then that data will be added to the subject's record.

The intravenous site will be assessed for patency and signs of local irritation prior to the start of the infusion, every 30 minutes during infusion, and at the end of study drug infusion.

Doses 2-5 are scheduled for study days 4, 7, 11 and 14 respectively in all cohorts. If the subject is unable to be dosed on the specified day, a window of $\pm$24 hours is acceptable. However, there must be a minimum of two days between any two doses. The calendar date and 24-hour clock time of the beginning and end of each infusion will be recorded on the CRF. The dates and timing of PK sampling around dose 5 will be adjusted for any change in dosing schedule.

It is the responsibility of the clinical investigator to ensure that all study drug received at the site will be inventoried and accounted for throughout the study. Study drug must be handled strictly in accordance with the protocol and the container label and will be stored in a limited access area under appropriate environmental conditions. The investigator agrees neither to dispense the study drug from, nor store it at any site other than the study site locations agreed upon with the sponsor. Study drug should be dispensed under the direction of the investigator.

Study drug will be supplied only to subjects participating in the study. Study drug may not be relabeled or reassigned for use to other subjects. The dispensation and use of study drug must be documented on the Drug Accountability Form. Used and unused study drug must be available for verification by the sponsor's site monitor during on-site monitoring visits. The destruction or return to the sponsor of used or unused study drug will be approved by the sponsor and documented on the Drug Return Form.

4 STUDY EVALUATIONS

4.1 Medical Questionnaires

Two questionnaires are provided - one designated for the mother and XLHED-affected neonate (Appendix 3) and one designated for male siblings of an enrolled neonate (Appendix 4). The former includes family history related to XLHED, pregnancy, labor and delivery, and neonatal data. The latter includes general medical history with an emphasis on issues common to XLHED-affected males. This questionnaire will be used for both affected and unaffected male siblings.

4.2 Pharmacodynamic/Efficacy Evaluations

Assessment of PD/efficacy endpoints will be performed on all subjects. The Sponsor will provide any equipment and training required for assessments.

4.2.1 *Growth and Development*

Cross-sectional data in patient populations with hypohidrotic ectodermal dysplasia consistently reports poor growth in infancy, most commonly poor weight gain and feeding issues, and an elevated risk of abnormal development (Clarke et al., 1987; Motil et al., 2005; Blüschke et al., 2010). The growth assessments will consist of feeding history as well as measurements of weight, length, and head circumference taken at study visits as part of the physical examination and plotted on standardized growth curves for males. The initial physical examination will include assessment of standard developmental milestones, and will be augmented at Months 2, 4 and 6 by a validated, standard of care infant assessment tool. Examples of such tools include but are not limited to the Bayley Scales of Infant Development II (BSID-II) and III (BSDI-III) and the Denver Development Screening Test II (DDST II) (Black and Matula, 2000). Whichever tool is selected should be designed for down to age 2 months of life and should be used for all follow-up visits.

4.2.2 *Thermoregulation*

XLHED-affected neonates and infants have a well-documented abnormality of thermoregulation (heat intolerance) and as a consequence are at elevated risk for life-threatening hyperthermia under unmonitored conditions (Clarke et al., 1987; Blüschke et al., 2010). At present there are no validated genetic, clinical or physiologic markers that identify the level of risk for a given XLHED-affected patient. In this protocol, assessment of thermoregulatory risk for an XLHED-affected neonate will provide valuable information for the family in preparing for a safe transition to home. Additionally, demonstration in the long-term extension study of an improved and sustained thermoregulatory improvement may be a key efficacy element in the response to study drug. Thus it is a relevant and appropriate evaluation in this protocol to assess thermoregulation of study subjects under closely monitored conditions with direct physician observation.

Thermoregulation reflects both sweat and insensible losses from the respiratory tract, both organ systems with compromised function in XLHED (Chawla et al., 2008; Clarke et al., 1987; Zankl et al., 2001; Casal et al., 2007; Seeliger et al., 2005). For term newborns placed inside a heated isolette, there is a wealth of validated clinical data on how to perform thermoregulation studies safely and what are the normal response parameters (e.g. Hey, 1975; Sjors et al., 1997; Stothers and Wagner, 1984; Sulyok et al., 1976). Healthy term babies reach the point of having to sweat to maintain body temperature at an isolette temperature of approximately 34°C. For thermoregulation assessment the study subjects will be placed unbundled in an isolette at a starting temperature of no more than 33°C in the ICU with continuous vital sign monitoring including respiratory rate, heart rate and body temperature. Isolette temperature will be held at the starting temperature for 0.5 hours for initial adaptation and baseline vital signs, following which it will be raised stepwise by 1-1.5°C every 30 minutes until reaching 36.5°C to assess infant response (Rutter and Hull, 1979). Total observation time is anticipated to be no more than 3 hours.

Strict stopping criteria will be in effect including: (1) a body surface temperature of $\geq$37.9°C (Rutter and Hull, 1979); (2) a noticeable change in behavior, e.g. uncontrolled crying; or (3) a sustained heart rate or respiratory rate outside of the normal range (HR 120-160 per minute; respiratory rate 40-60 per minute; Cloherty et al. 2004). With any of these changes or at the discretion of the study physician monitoring the assessment, the subject will be removed from the isolette to an unheated observation table until all vital signs and physical examination return to Baseline. Additional interventions are not anticipated, but will be at the discretion of the monitoring physician and the ICU staff.

In this exploratory endpoint, each subject's pre-dosing response to this short and controlled environmental challenge will be compared with the published literature and with the result of thermoregulation assessment after EDI200 dosing. Additional assessments of thermoregulation and heat tolerance are not standardized for ages 2-6 months but will be included as efficacy endpoints in the long-term extension study.

4.2.3 *Eccrine Structures*

4.2.3.1 Sweat Duct Density

Sweat duct density (number/cm^2) from at least two different sites on the soles of the feet (newborns and infants) or palms (siblings age $\geq$1 year) will be determined through analysis of images collected by direct visualization with an approved device, the Lucid VivaScope 1500 (www.lucid-tech.com). This technology has been tested in controls and XLHED-affected males from the newborn period to adulthood without complication (Dietz et al., 2013; Huttner et al., 2012; ECP-005 Clinical Study Report). An adhesive ring will be placed on the subject's palm/sole to which the VivaScope will be attached via a magnetic lock. A series of photographs will be taken of an area

approximately 6mm X 6mm. An individual trained in the use of this device will be involved in the acquisition of all images.

Up to two independent image readers trained in the reading of VivaScope images will interpret the images and provide sweat duct counts for inclusion with the study data. If there is a discrepancy in their counts of 10% or greater on an individual image, then both readers will reinterpret the same image and a final assessment made as an average of the repeat sweat duct counts. To account for growth during the study, all sweat duct counts will be adjusted for body surface area (Haycock et al, 1978).

4.2.3.2 Sweat Rate Testing

Sweat rate assessment following cholinergic stimulation is a technique used commonly in clinical trials as reported for the evaluation of distinct conditions including orthostatic hypotension, diabetes, growth hormone deficiency, Parkinson's disease, hypohidrosis, and Fabry's disease (Itoh et al., 2003; Low et al., 1983; Ramaswami et al., 2007). Maximal sweating on the volar lower arm surface of each subject will be induced by pilocarpine iontophoresis followed by sweat collection using the Macroduct Sweat Collection System developed primarily for sweat collection and analysis in the diagnosis of Cystic Fibrosis from the newborn period on (www.wescor.com). The Collection System consists of the Webster Sweat Inducer, Pilogel® Iontophoretic Discs and Macroduct Sweat Collectors. The Macroduct Sweat Collection System is approved for subjects of all ages including neonates (Mastella et al., 2000) and the manufacturer provides adequate directions for the device's use.

Pilogel® Iontophoretic Discs are unique gel reservoirs of pilocarpinium ions that are simple and safe to use in the iontophoretic stimulation of sweat. A Pilogel® disc is inserted into each of the recessed stainless steel electrodes, which are then attached to the subject. The Webster Sweat Inducer is activated by a start switch subsequently delivering a safe and optimal quantity of pilocarpine for gland stimulation (equivalent to five minutes iontophoresis at 1.5 mA) followed by an automatic, programmed stop.

Following completion of the pilocarpine iontophoresis the Webster Sweat Inducer electrodes and discs are removed from the subject, the application site is wiped once with alcohol, and a Macroduct Sweat Collector is placed over the site of one electrode. The Macroduct Sweat Collector is held in place for approximately 30 minutes using a Velcro Macroduct Strap. Sweat volume is determined from microliter markings on a collection coil diagram.

Individuals trained in the use of the Macroduct Sweat Collection System will be involved in both procedures and the acquisition of the data. The manufacturer of the

iontophoresis device does report the rare occurrence (1 in 50,000) of small skin burns at the site of application, and physicians will be available on site to evaluate any adverse event occurrence.

4.2.4 *Pulmonary Function Testing and eNO levels*

Pulmonary function testing will be performed in the sibling sub-study on all subjects age 5 years and older at a laboratory experienced with pediatric subjects. Additionally, levels of exhaled nitric oxide (eNO) as an indicator of pulmonary inflammation will be quantified non-invasively with an age-group appropriate device in all siblings age 4 years and older.

4.2.5 *Dry Eye Assessment*

The eye examination will be performed by an ophthalmologist experienced in assessments of tear film and ocular surface in infants as well as children and adults. In newborns and infants, the examination will document the presence/absence of signs of infection and irritation, as well as a tear film break-up time. For children 5 years or older (sibling sub-study) the assessment will also include the Shirmer test for rate of tear production and the OCULAR SURFACE DISEASE INDEX© questionnaire (Appendix 5).

4.2.6 *Skin Biopsy*

Three mm diameter punch biopsies of skin will be obtained from the upper outer thigh area. Sites will follow their institutions standard practice with regard to biopsy procedure. The biopsy site may require absorbable suture(s). RNA isolated from the skin biopsies will be assayed in expression analyses to establish a biochemical response to EDI200 treatment in these EDA-deficient subjects. Genes to be evaluated include but are not are not limited to those involved in the EDA/EDAR pathway, e.g. EDAR, CTGF (connective tissue growth factor), Shh (sonic hedgehog) and Lgr5 (leucine-rich G-protein coupled receptor). For each study subject, comparisons will be made between the expression profiles obtained at Baseline, after the first and the last dose of EDI200.

4.2.7 *Dental Imaging/Examination*

The absence of tooth buds is a key confirmatory finding in phenotype assessment of an XLHED-affected neonate and can be determined from a lateral radiograph (Swischuk, 2003). Radiation exposure will be minimized in this study with a single lateral film at Baseline. Follow-up radiographs will be included in the long-term extension study for PD/efficacy documentation (first follow-up expected at age 2 years). Radiographs are the preferred imaging modality as they detect tooth bud mineralization but do not require sedation in the infant.

The sibling sub-study includes a dental examination that is brief and age-appropriate involving an assessment of tooth count and tooth shape. No X-ray exposure will be involved.

4.3 Genetic Testing

To meet inclusion criteria for EDI200 administration, potential study subjects are required to have their XLHED diagnosis confirmed by genetic testing of the EDA gene and these test results relayed to the study site. EDA genetic testing itself is outside of the scope of this protocol. If requested, the families of prospective subjects in need of EDA genotyping will be referred to resources available to facilitate this testing. Consent from the family (written or verbal) will be obtained as part of the screening process to provide the study site with documentation of genetic testing results via a secure and confidential method including an option for electronic transmission.

It has been demonstrated that a polymorphism in the EDAR gene associated with increased activity may be associated with amelioration of some XLHED-symptoms (Cluzeau et al., 2012). As this has the potential to impact outcome measures, all participating neonates will be tested for this specific polymorphism, c.1540T>C, rs3827760, p.V370A. The testing may be performed on the prior DNA sample used for EDA genotype confirmation, although results are not required prior to the initiation of dosing.

4.4 Digital Facial Photographs

A facial recognition software algorithm is under development that will identify characteristics of XLHED-affected males as neonates, children and adults. The algorithm uses non-invasive 2D frontal photographs and will be used in this study to document the newborn facial appearance as well as changes in craniofacial appearance over time, including the long-term extension study. Facial frontal and lateral digital images will be obtained with a commercial camera, and all photographs will be anonymized prior to transmission for analysis to FDNA, the company developing the software algorithm (http://www.fdna.com).

4.5 Clinical and Safety Laboratory Evaluations

4.5.1 *Safety Laboratory Sampling*

Laboratory parameters measured at the study site will include a complete blood count (RBC, WBC, hemoglobin and hematocrit) with differential and platelet count, serum chemistries including glucose, electrolytes (Na, K, Cl, Ca), total protein and albumin, assessment of hepatic and renal function (BUN, serum creatinine, AST, ALT and alkaline phosphatase), and urinalysis (dipstick and microscopy). It will be the Principal Investigator's responsibility to assess laboratory parameters against local reference ranges and to assess the clinical significance of any out-of-range values.

4.5.2 *Pharmacokinetic Sampling*

Analysis will be performed to characterize EDI200 PK after the doses designated as dose #1 and #5. Blood samples (0.25 ml) for determination of EDI200 in plasma will be taken into collection tubes without additives on the days and times indicated. The model used to determine frequency of pharmacokinetic sampling incorporates a sparse sampling approach in order to reduce the number of blood samples required for each subject. Note that additional PK samples are scheduled for age 2 and 6 months to assess study drug persistence at low levels as was reported for XLHED adults.

PK samples will be drawn at approximately the following time points pre-dose (defined as prior to the start of infusion) and post-dose (defined as after infusion is completed):

	Pre-Dose	Post-Dose							
		15 (±5) min	3 (±.5) hrs	8 (±1) hrs	18 (±2) hrs	24(±2) hrs	48 (±4) hrs	168(±8) hrs	Age 2 months (±1 wk) & 6 months (±2 wks)
D0 (dose 1)	X	X	X	X		X	X		
D14 (dose 5)	X	X	X		X		X	X	X

Immediately upon sampling, the sample will be identified with a label bearing details of the study number, subject number, sampling time point, and a sample type. The sample will be separated by centrifugation at rotation 1500xg, 4°C for 10 minutes. Two 50 ul aliquots of serum will be transferred to polypropylene tubes labeled identically to the original blood sample and stored at approximately -70°C pending analysis. The time at which samples are taken, received into the separating room and placed in the freezer will be recorded in the study documentation.

4.5.3 *Immunogenicity Sampling*

Blood samples (~0.25 mL per sample) for immunogenicity sampling will be taken into serum separator tubes on the days indicated.

Immediately upon sampling, the sample will be identified with a label bearing details of the study number, subject number, sampling time point, and a sample type. The sample will be separated by centrifugation. Two equal aliquots of serum will be transferred to polypropylene tubes labeled identically to the original blood sample and stored at approximately -70°C pending analysis. The calendar date and 24-hour clock time at which samples are taken, centrifuged and placed in the freezer will be recorded in the study documentation.

4.5.4 *Total of Blood Volume*

The approximate number of safety laboratory evaluations and the approximate volume of blood that will be collected per subject throughout the study are as follows:

All Subjects	Genetic Testing (5 ml)*	Safety Labs (1.5 ml)	Immunogenicity (0.25 ml)	PK (0.25 ml)	Total Blood Volume (ml)	ml/kg (3.5 kg neonate)
Screening	0	0	0	0	0.00	
Baseline	1 x 5 = 5.0	1 x 1.5 = 1.5	1 x 0.25 = 0.25	0	6.75	1.93
Week 1	0	1 x 1.5 = 1.5	0	6 x 0.25 = 1.50	3.00	0.86
Week 2	0	0	0	0	0	0
Week 3	0	1 x 1.5 = 1.5	1 x 0.25 = 0.25	5 x 0.25 = 1.25	3.00	0.86
Week 4	0	1 x 1.5 = 1.5	0	1 x 0.25 = 0.25	1.75	0.50
Months 2,4,6	0	2 x 1.5 = 3.0	2 x 0.25 = 0.50	2 x 0.25 = 0.50	4.00	
Total	1 x 5 = 5.0	6 x 1.5 = 9.0	4 x 0.25 = 1.0	13 x 0.25 = 3.25	18.25	

* For testing of the EDAR polymorphism in the case that DNA is not available from prior genotyping

4.6 Safety Evaluations

The safety evaluations will consist of adverse events, concomitant medications, vital signs, weight, physical exam findings, and safety laboratory values. Adverse events will be recorded starting when the treatment Informed Consent document (ICF2) is signed and continuing until all study assessments are completed (including Month 6 follow-up evaluations for all AEs, and Month 6 + 28 days for SAEs). Information on the definition, characteristics, and reporting requirements are provided below.

4.6.1 *Adverse Events*

4.6.1.1 Definition

An adverse event (AE) is any reaction, side effect, or other untoward event (signs, symptoms, or changes in laboratory data) associated with participation in this study, whether or not the event is considered related to the study or any of the procedures being conducted. All AEs occurring after signing the informed consent document will be recorded. AEs will be ascertained on the basis of volunteered symptoms and clinical observation. AEs will be recorded during the study on the appropriate CRF page. All AEs considered to be related to study procedures, and all

serious adverse events (SAEs; see Section 4.5.2) will be followed until resolved or until a stable status has been achieved. SAEs will be recorded up to 28 days following the Day 168 visit.

4.6.1.2 Reporting Adverse Events

Any adverse event (AE, a clinical sign, symptom, or disease) temporally associated with this study, whether or not considered related to study drug, shall be documented on the case report form (CRF). All AEs reported by the subject or observed by the PI will be individually listed. The signs and symptoms, the date of onset, duration, and relationship to study drug, action taken, and follow-up procedures will be reported.

4.6.1.3 Relationship

The relationship between an AE and the administration of study drug or the procedures employed in this study will be determined by the PI on the basis of his or her clinical judgment and the following definitions:

Definitely Related: Follows a reasonable temporal sequence from administration of study drug; follows a known response pattern to the study procedure; and, when appropriate to the protocol, is confirmed by improvement after stopping the study procedure (positive re-challenge) and by reappearance of the reaction after repeat exposure (positive re-challenge); and cannot be reasonably explained by known characteristics of the participant's clinical state or by other therapies.

Probably Related: Follows a reasonable temporal sequence from administration of study drug; follows a known response pattern to the study procedure; and, when appropriate to the protocol, is confirmed by improvement after de-challenge; and cannot be reasonably explained by the known characteristics of the participant's clinical state or by other therapies.

Possibly Related: Follows a reasonable temporal sequence from administration of study drug and follows a known response pattern to the study procedure but could have been produced by the participant's clinical state or by other therapies.

Unlikely Related: The reaction has little or no temporal sequence from administration of the study drug, and/or a more likely alternative etiology exists.

Not Related: Sufficient information exists to indicate that the etiology is unrelated to administration of study drug in this study. Two or more of the following variables apply:

- The AE does not follow a reasonable temporal sequence with occurrence of administration of study drug;
- The AE is readily explained by the participant's clinical state or other therapies.

4.6.1.4 Severity

The intensity of an AE, as determined by the PI, will be assessed and graded utilizing a 5-point scale according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v4.0). It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under section 4.6.2. If a subject experiences the same AE with more than one level of intensity, the highest level of intensity should be recorded on the CRF. The severity grading will be reported in the eCRF as follows:

Grade 1 = **Mild;** asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 = **Moderate**; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
Grade 3 = **Severe** or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
Grade 4 = **Life-threatening** consequences; urgent intervention indicated.
Grade 5 = **Death** related to AE.

4.6.1.5 Outcome

The outcome of an AE will be assessed as follows:

- Resolved
- Unresolved
- Resolved with sequelae
- Death
- Unknown

4.6.2 *Serious Adverse Event*

4.6.2.1 Serious Adverse Event Definition

An SAE is any AE that results in any of the following outcomes:

- Death
- A life threatening AE
    - The term "life-threatening" means that the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe
- An inpatient hospitalization or prolongation of existing hospitalization (24 hours or more)
- A persistent disability/incapacity, or a
- A congenital anomaly/birth defect

- Important medical event

An important medical event may not result in death, be life threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

4.6.2.2 Serious Adverse Event Reporting

The PI will report all SAEs to the Sponsor in a timely fashion, within 24 hours of awareness, by completing and faxing the SAE Report Form to CTI Safety as per directions described in the Study Reference Manual. The reporting PI is obligated to provide their initial assessment of the relationship between study drug and the occurrence of each SAE. Determination of expectedness and the reporting of the SAEs to relevant regulatory authorities will be determined by the Sponsor. The reporting PI is responsible for reporting all SAEs to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) as required by the appropriate regulations.

Based on the investigator's assessment of causality of the adverse event and discussions with the medical monitor, a decision will be made by the sponsor concerning the need for further action with respect to the future conduct of this trial. The primary consideration governing further action is whether new findings affect the safety of other subjects participating in the clinical study. If the discovery of a new adverse event related to study drug raises concerns over the safety of its continued administration to subjects, the sponsor or designee will take immediate steps to notify the Data Safety Monitoring Board (DSMB), the regulatory authorities and all the investigators participating in clinical studies of the study drug.

The Sponsor will notify the relevant regulatory authorities according to Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) regulations. The reporting PI will notify the Sponsor through the following contact:

Name:	CTI Global Drug Safety & Pharmacovigilance
Address:	10123 Alliance Road Cincinnati, OH 45242
Telephone:	1-877-755-0742
Fax:	1-866-215-5862
E-mail:	CTISafety@ctifacts.com

Additional SAE follow-up information, if required, should all be faxed to CTI Safety within 24 hours of receipt. The follow-up information should be documented on the original SAE Report Form following Good Documentation Practices and faxed with any additional relevant source documentation. Additionally, the AE eCRF should be updated accordingly to match the SAE Report form.

SAE source documentation requested may include; discharge summary, diagnostic test results, consultation reports, relevant specimen cultures, diagnostics, or laboratory values. The investigator must ensure that all source documentation maintains each subject's anonymity. The site and subject number must be documented on every page, the subject's name replaced by the subject's study number, and all other protected health information should be redacted (e.g. social security number, medical record number, room number, etc.).

Compliance with the requirements for expedited reporting is essential. The sponsor or the sponsor's designee is responsible for informing the regulatory authorities as well as all other participating investigators of the following events:

- Any event associated with the use of the study drug, that is both serious and unexpected (SUSAR), or
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.

The sponsor or designee will expedite the reporting of all SUSARs to the appropriate regulatory authorities and the Institutional Review Board/Independent Ethics committee (IRB/IEC). The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse event (AE). For fatal or life threatening cases, the term will be a maximum of 7 calendar days for a preliminary report with another 8 calendar days for completion of the report. The sponsor or designee will also inform all investigators of such events.

The sponsor or designee will provide expedited reports of the following SUSARs to the IRB/IEC:

- SUSARs that have arisen in the clinical trial that were assessed by the EC
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that were assessed by the EC.

4.7 Concomitant Medication

There are no concomitant medications that are excluded from this study. There are no concomitant medications known to interact with EDI200.

4.8 Data Safety Monitoring Board (DSMB)

An independent DSMB will be established to monitor the safety of treated subjects. A European member has been added to the same DSMB in place for the Phase 1 adult safety study (ECP-004) to monitor this neonate trial. All safety-related laboratory values will be available to the DSMB in real time. At the scheduled DSMB review meetings, detailed safety reviews will be provided to the DSMB including; adverse events, concomitant medications, infusion/injection

site reactions, physical examination, weights and vital signs, and all PK and safety laboratory values. Scheduled DSMB meetings include the following:

- After dosing is completed in XLHED neonate cohort 1, the DSMB will meet and review safety and PK data from all cohort 1 subjects prior to initiation of dosing in XLHED neonate cohort 2. The timeframe for this review is approximately three weeks following dosing of the last cohort 1 subject. The cohort 1 PK data review is intended to confirm that the exposure levels in the cohort as a whole and for each subject were within the limits associated with safe study drug administration in the preclinical GLP toxicology studies, and that the expected exposure with dose escalation in cohort 2 will remain in the range that was safe and well tolerated. Additionally, the DSMB will review safety and PK data obtained from adult cohort 2 (NCT01564225, www.clinicaltrials.gov) dosed at the same 10 mg/kg/dose as is proposed for neonate cohort 2.
- After dosing is completed in XLHED cohort 2, the Sponsor may elect to enroll a third cohort with EDI200 dosing at 20 mg/kg/dose. Prior to initiating dosing of this third cohort, the DSMB will review safety and PK data from cohorts 1 and 2 in order to provide guidance on advancing to dosing at the higher level.
- At the end of the Study, DSMB will review and summarize all study safety data. DSMB summaries will be provided in a timely fashion to the Sponsor.

Unscheduled DSMB reviews will take place as outlined in Section 3.3.4-3.3.7 for single or accumulated adverse events. Additional safety-related evaluations of one or more subjects may be requested by the DSMB based on findings through the 6-month, end-of-study visit.

5 SCHEDULE OF STUDY ASSESSMENTS

5.1 Screening – End of first trimester through DOL #12

- Medical history related to XLHED in the family and for pregnancy, labor and delivery
- Verbal consent from both parents (if reasonably available) to provide documentation of genetic testing results to the study site by a secure and confidential method including the option for electronic transmission
- Inclusion/Exclusion criteria will be confirmed for parents and fetus/neonate

**A screening call may be conducted to assess eligibility for study participation, inclusion/ exclusion criteria, and availability of EDA genetic test results. If prior genotyping is not available, either cord blood or a neonatal blood sample may be sent to an accredited laboratory for testing.*

5.2 Baseline – DOL #2 through DOL #14

- Transport Informed Consent from both parents (if reasonably available) if neonatal transport to the study site is to be provided as part of the study
- Treatment Informed Consent from both parents (if reasonably available) for study procedures and study drug administration
- Confirmation of inclusion/exclusion criteria
- Updated medical history
- Full physical examination
- Blood draws for safety laboratories, EDAR gene V370A polymorphism testing, PK and immunogenicity
- Bioactivity assessments
    - Growth and development
    - Dental imaging
    - Digital facial photograph
    - Sweat duct density
    - Sweat rate
    - Dry eye assessment
    - Thermoregulation
    - Skin biopsy sample for molecular profiling
- Adverse Events & Concomitant Medications

5.3 Treatment

Day 0

- Brief physical exam (prior to dosing)
- Study drug administration (dose 1)
- Vital sign monitoring during and for 24 hours following study drug infusion
- Blood draw for PK analysis at the following timepoints:
    - Post-end of infusion timepoints: 15 min, 3 and 8 hours
- Adverse Events & Concomitant Medications

Day 1

- Brief physical exam
- Blood draw for safety laboratory evaluations
- Blood draw for PK analysis at the following timepoints:
    - 24 hours post dose 1
- Skin biopsy 24 hours post dose 1
- Adverse Events & Concomitant Medications

Day 2

- Blood draw for PK analysis at the following timepoints:
    - 48 hours post dose 1
- Adverse Events & Concomitant Medications

Day 4

- Brief physical exam (prior to dosing)
- Study drug administration (dose 2)
- Vital sign monitoring during and for 24 hours following study drug infusion
- Adverse Events & Concomitant Medications

Day 7

- Brief physical exam (prior to dosing)
- Study drug administration (dose 3)
- Vital sign monitoring during and for 24 hours following study drug infusion
- Adverse Events & Concomitant Medications

Day 11

- Brief physical exam (prior to dosing)
- Study drug administration (dose 4)
- Vital sign monitoring during and for 24 hours following study drug infusion
- Adverse Events & Concomitant Medications

Day 14

- Brief physical exam (prior to dosing)
- Study drug administration (dose 5)
- Vital sign monitoring during and for 24 hours following study drug infusion
- Blood draws for PK analysis at the following timepoints:
    - Pre-dose and the following post-end of infusion timepoints: 15 minutes, 3 and 18 hours
- Adverse Events & Concomitant Medications

Day 15

- Brief physical exam
- Skin biopsy for molecular profiling (24 hours after study drug administration)
- Adverse Events & Concomitant Medications

Day 16

- Blood draw for PK analysis at the following timepoints:
    - 48 hours post dose 5
- Blood draw for safety laboratory evaluations
- Blood draw for immunogenicity testing
- Adverse Events & Concomitant Medications

Day 21

- Full physical exam
- Blood draw for safety laboratory evaluations
- Blood draw for PK analysis at the following timepoints:
    - 168 hours post dose 5
- Thermoregulation assessment
- Adverse Events & Concomitant Medications

**If any visits are adjusted during the baseline and/or treatment portions of the study (if a subject is seen or dosed earlier or later than what is described in the protocol) then all subsequent visits (if applicable) should be adjusted accordingly.*

5.4 Post-Treatment

Follow-Up Visit 1 – Month of Life 2 (±1 week)

- Full physical exam
- Blood draw for safety laboratory evaluations
- Blood draw for immunogenicity testing
- Blood draw for PK
- PD/efficacy assessments
    - Growth and development

    - Sweat rate
- Adverse Events & Concomitant Medications

Follow-Up Visit 2 – Month of Life 4 (±1 week)

- Full physical exam
- PD/efficacy assessments
    - Growth and development
- Adverse Events & Concomitant Medications

End-of-Study Visit – Month of Life 6 (±2 weeks)

- Full physical exam
- Blood draw for safety laboratory evaluations
- Blood draw for immunogenicity testing
- Blood draw for PK
- PD assessments
    - Growth and development
    - Digital facial photographs
    - Sweat duct density
    - Sweat rate
    - Dry eye assessments
- Adverse Events & Concomitant Medications

5.5 Unscheduled Visits

The Sponsor or DSMB may request unscheduled visits either during the subject's participation in the Study or after his completion. The unscheduled visits may include additional safety-related evaluations (including blood sampling) based on findings through the 6-month, end-of-study visit.

6 STATISTICAL METHODS

6.1 Sample Size

The sample size is based on clinical and practical considerations for a Phase 2 study in an ultra-rare genetic disorder with enrollment limited to newborns. It is considered to be appropriate to meet the objectives of the study while minimizing the exposure of volunteers. Each cohort is anticipated to enroll approximately 3-7 XLHED-affected neonates. No more than 15 subjects total will be enrolled.

6.2 Analysis Datasets

The safety analysis set will consist of all subjects who receive at least one dose of study medication. The PK analysis set will consist of those subjects who receive at least one dose of study medication and have sufficient concentration data to obtain a plasma concentration by time profile. The PD/efficacy analysis set will consist of all subjects who receive at least one dose of study medication and complete the follow-up assessments through at least month 2. No missing data will be replaced by values carried forward.

6.3 Primary and Pharmacodynamic/Efficacy Assessments

The safety assessment variables are AEs, concomitant medications, vital signs, weight, physical examination findings, hematology, clinical chemistry, and urinalysis laboratory test results.

The PK assessment variables will be the following derived PK parameters for EDI200:

- C_{max}, T_{max}, $AUC_{0\text{-}tau}$
- Other PK parameters including but not limited to clearance rate may also be examined.

The medical history and clinical evaluations for the sibling sub-study will be tabulated and intra-familial comparisons will be made with data obtained from the neonate subjects receiving study drug.

The following pharmacodynamic/efficacy outcomes will be monitored in all subjects receiving study drug:

- Growth and development
- Dentition (follow-up radiographs in extension study)
- Craniofacial development by digital photography
- Sweat duct density
- Sweat rate
- Dry eye signs and symptoms
- Thermoregulation
- Molecular expression profile of skin biopsy tissue

6.4 Pharmacodynamic/Efficacy Variables (not including sibling sub-study)

Growth and Development
Testing to be performed at Baseline, Months of Life 2, 4, and 6:

- Weight, length, head circumference plotted on standardized growth curves for males
- Developmental assessments

Dental Imaging:
Testing to be performed at Baseline:

- Lateral jaw film

Craniofacial Development
Testing to be performed at Baseline, and Month of Life 6

- Digital facial photographs

Sweat Duct Density
Testing to be performed at Baseline and Month of Life 6:

- Sweat ducts per 36 mm^2 on confocal microscopy image

Sweat Rate:
Testing to be performed at Baseline, Months of Life 2 and 6:

- Volume of induced sweat collected over 30 minutes following pilocarpine iontophoresis

Dry Eye Assessments:
Testing to be performed at Baseline and Month of Life 6:

- Examination for signs of infection and/or irritation, as well as tear film break-up time

Thermoregulation
Testing to be performed at Baseline, TD21:

- Clinical and vital sign response to isolette temperature range

Skin Biopsy for Molecular Expression Profile:
Testing to be performed at Baseline, TD1 (approximately 24 hours after 1st dose) and TD15 (approximately 24 hours after last dose):

- Analysis of gene expression on skin biopsy samples

6.5 Analysis of Safety and Pharmacokinetic Variables

Safety variables will be tabulated and presented for all subjects receiving one or more doses of EDI200. Change from Baseline over time will be presented by cohort for continuous variables including laboratory values and vital signs using descriptive statistics with n, mean, standard

deviation, minimum, median and maximum as appropriate. Shift tables will be presented. Out-of-range values will be flagged in the data listings and will also be presented separately.

AEs will be coded using the current MedDRA drug dictionary version. Only treatment emergent AEs will be included in the summary tables. The incidence of subjects reporting AEs will be summarized by system organ class, preferred term, severity and relationship to study drug.

The PK parameters of EDI200 will be listed and summarized by dosing cohort. Mean and individual plasma concentration-time curves will be presented on both linear and semi-logarithmic scales. The derivation of the PK variables from the EDI200 plasma concentrations will be determined using WinNonlin Professional v5.2, or higher. The PK parameters of EDI200 will be listed and summarized.

6.6 Statistical Methods

Individual subject values for EDA genotype and all endpoints, both at Baseline and across time, will be provided. Demographics for the entire study dataset will be presented using descriptive statistics. Table summaries of Baseline values for all endpoints will be provided for the following groups: all subjects and each dosing cohort. Descriptive statistics will be provided across time for each cohort with n, mean, standard deviation, minimum, median and maximum as appropriate.

6.7 Data Management

As outlined in section 7.5 the Sponsor or designee will forward questions regarding missing data or discrepancies to the PI.

The original terms used in the case report forms by the PI to identify adverse events will be coded according to the MedDRA dictionary. The percentage of subjects with adverse events will be tabulated overall and by the MedDRA body system and preferred term.

7 STUDY ADMINISTRATION

7.1 Protocol Modifications

Neither the PI nor Sponsor will modify this protocol without obtaining the concurrence of the other. All protocol amendments must be issued by the Sponsor, signed and dated by the PI, and should not be implemented without prior IRB/IEC approval, except where necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study (e.g., typographical errors, inconsistencies).

In situations requiring a departure from the protocol, the PI or other physician in attendance will discuss with the appropriate Sponsor representative. This contact will be made before implementing any departure from protocol. In all cases, contact with the Sponsor will be made as soon as possible in order to discuss the situation and agree on an appropriate course of action. Any departure from the protocol and the circumstances requiring it will be documented.

7.2 Monitoring

The Sponsor or their designee (hereby referred to as “Monitor”) will monitor all aspects of the study as required by GCP and any existing standard operating procedures for compliance with applicable regulations. These individuals will have access to all records necessary to ensure integrity of the data and will review progress of the study with the PI.

The monitor will compare the data entered into the CRF’s with any source documents. The nature and location of any source documents will be identified in advance. This will ensure that all sources of original data required to complete the CRF are known to the Sponsor and investigational staff; and are accessible for verification by the Monitor. If electronic records are maintained, the method of verification must be discussed with the investigational staff. At a minimum, source documentation must be available to substantiate subject identification, eligibility and participation, proper informed consent procedures, adherence to protocol procedures, record of safety parameters, adequate reporting and follow-up of adverse events, completion and reason of withdrawal/ termination. Specific items required as source documents will be reviewed with the PI before the study. The author of an entry in the source documents will be identifiable.

If any data are recorded directly into the CRF, at a minimum there should be an entry in the source document that each of the assessments was done, and by whom and the date it was done. The author of an entry in the source documents must be identifiable. The CRF data will be entered into an appropriate data storage system and verified for accuracy.

Direct access to source documentation must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. Findings from this review of CRF’s and source documents will be discussed with the investigational staff. The Sponsor

expects that, during monitoring visit(s), the relevant investigational staff will be available, the source documentation will be available, and a suitable environment will be provided for review of study-related documents. The monitor will provide feedback on the study conduct to the PI.

The investigator will permit trial-related monitoring, audits, audits, IRB/IEC review, and regulatory inspection(s), and providing direct access to source data/documents.

7.3 Ethic Aspects

7.3.1 PI Responsibilities

The PI is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines, Good Clinical Practice (GCP), and applicable regulatory requirements.

GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well being of study subjects are protected, consistent with the principles that have originated in the Declaration of Helsinki and that the clinical study data are credible.

7.3.2 Institutional Review Board/Independent Ethics Committee

The PI will provide the Institutional Review Board/Independent Ethics committee (IRB/IEC) with all requisite material, including a copy of the protocol, informed consent and all subject materials. The study will not be initiated until the IRB/IEC provides written approval of the protocol and the informed consent and the PI has obtained documents approved by the IRB/IEC. Any reports requested on the progress of this study by the PI will be made to the IRB/IEC and the Sponsor.

7.3.3 Informed Consent

A properly executed, written informed consent in compliance with national and local regulations and GCP guidelines will be obtained from each subject prior to entering the study or performing any study-related procedure.

The PI will submit a copy of the informed consent document to the IRB/EC for review and approval before research subjects are enrolled. The PI will provide a version of the signed informed consent to the subject and a signed version will be maintained in the subject's research record.

7.3.4 Confidentiality of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the safety, quality, and utility of the procedures performed during this study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

The Sponsor ensures that the personal data are:

- Processed fairly and lawfully
- Collected for specified, explicit, and legitimate purposes and not further processed in a way incompatible with these purposes
- Adequate, relevant, and not excessive in relation to said purposes
- Accurate and, where necessary, kept up to date

Explicit consent for the processing of personal data will be obtained from the participating subject before collection of data. Such consent should also address the transfer of the data to other entities and to other countries, if applicable.

The subject has the right to request through the PI access to his/her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps should be taken to respond to such request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel and designees whose responsibilities require access to personal data agree to keep the identity of study subjects confidential.

7.4 Subject Identification Register

The PI agrees to complete a subject identification register to permit easy identification of each subject during and after the study. The Monitor will review the document for completeness.

The subject identification register will be treated as confidential and will be filed by the PI in the Regulatory Binder. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by initials and assigned number only.

7.5 Case Report Form Completion

All of the clinical data will be captured via electronic data capture (EDC) using an approved and validated EDC system. The investigator site staff will enter and edit the data via a secure network, with secure access features (username, password and secure identification – an electronic password system). A complete electronic audit trail will be maintained.

The investigator will approve the data using an electronic signature, and this approval is used to confirm the accuracy of the data recorded (CFR 21, Part. 11, 2011).

Electronic CRF's (eCRF) will be used for all patients. The investigator's data will be accessible from the investigator's site throughout the trial. The eCRFs must be kept current to reflect patient status at each phase during the course of the trial. The patients must not be identified on the eCRF by name. The appropriate coded identification (i.e. Patient Number) must be used. The investigator must make a separate confidential record of these details (subject identification record) to permit identification of all patients enrolled in a clinical trial in case follow-up is required.

Copies of the eCRF together with all data changes made will be supplied to the investigator at the end of the trial. The investigator will be responsible for retaining all records pertaining to the trial as specified in the appropriate contract.

7.6 Data Quality Assurance

Steps to be taken to assure the accuracy and reliability of data include the selection of a qualified PI, review of protocol procedures with the PI and associated personnel before the study, and a monitoring visit(s) by the Sponsor. Instruction for completion of CRFs will be provided and reviewed with study personnel before the start of the study. The Monitor will review CRFs for accuracy and completeness during the conference and/or during a monitoring visit(s). Any discrepancies will be resolved with the PI or designee, as appropriate. The data will be entered into an appropriate data storage system and verified for accuracy.

7.7 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

APPENDIX 1 – AUTOMATIC PHENOTYPE IDENTIFICATION OF XLHED PATIENTS

FINAL REPORT

Provided as a separate document.

APPENDIX 2 – THE NATIONAL CANCER INSTITUTE (NCI) COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS V4.0 (CTCAE)

VERSION 4.0

US DEPARTMENT OF HEALTH AND HUMAN SERVICES- NATIONAL INSTITUTES OF HEALTH-NATIONAL CANCER INSTITUTE

Provided as a separate document.

APPENDIX 3 – MEDICAL QUESTIONNAIRE FOR MOTHERS AND XLHED-AFFECTED NEONATES

Medical Questionnaire for Mothers and XLHED-Affected Neonates

Participant's Initials: ☐☐☐ **Can be left blank if choice of name is not yet finalized*

Today's Date: ☐☐/☐☐/☐☐☐☐

Date of birth: ☐☐/☐☐/☐☐☐☐
DD/MM/YYYY

Has the mother been diagnosed with HED? ☐Yes ☐No

If yes, age at diagnosis: ☐0-5 years ☐6-17 years ☐≥18 years

Does the mother have any family members diagnosed with HED? ☐Yes ☐No

If yes, check all that apply:
☐Mother
☐Father
☐Sisters
☐Brothers
☐Aunts
☐Uncles
☐Other

If other, specify:

Has the mother or any family member(s) had genetic testing for HED? ☐Yes ☐No

**Every attempt should be made to obtain a copy of the genetic test results. The results must be provided to the study site and will also be provided to the lab conducting your baby's genetic testing in order to expedite the testing process.*

Mother's age at delivery: ☐☐

What number pregnancy is/was this child for the mother? ☐☐

Is the mother currently pregnant? ☐Yes ☐No

Thinking of ***all*** of the mother's pregnancies to date, including this one, how many resulted in each of the following:

	Number
Miscarriage in the first trimester (up to 14th week of pregnancy)	☐☐
Miscarriage later in pregnancy	☐☐
Stillbirth	☐☐
Preterm birth (prior to 37 weeks)	☐☐
Full term birth (37 weeks or more)	☐☐

Did the mother have any of the following complication during ***this child's*** (the study subject) pregnancy? ☐Yes ☐No

If yes, please list treatment.

Diabetes: _____
High blood pressure: _____
Infections, fevers and illnesses: _____
Other problems/complications: _____

Medications used during pregnancy: _____
_____
Are any of these medications investigational? ☐Yes ☐No

Did the mother have any of the following?
☐Ultrasound
☐1st trimester screen/triple/quad screen
☐Amniocentesis or CVS

Were any results from this testing abnormal? ☐Yes ☐No

If yes, please explain:
_____
_____

Check here ☐ if your child is not born yet and do NOT complete the rest of this form.

The child was born:
☐Full-term
☐Prematurely (weeks premature: ☐☐)

If premature, please list the reason:
_____

The child was born: ☐Vaginally ☐By C-section
If by C-section, why: _____

Birth Hospital: _____

Birth location:

Country: _____
City: _____
State (if applicable): _____

Birth weight: ☐☐.☐☐ kg
Birth Length: ☐☐☐ . ☐☐ cm
Birth head circumference: ☐☐☐ . ☐☐ cm

Did your child have any problems after delivery or require admission to the Neonatal Intensive Care Unit (NICU)? ☐ Yes ☐ No

If yes, please explain:

_____

_____

Did he/she pass the:
Newborn metabolic screen: ☐ Yes ☐ No ☐ Unsure
Newborn hearing screen: ☐ Yes ☐ No ☐ Unsure

How many days old was child when he/she went home from the hospital? ☐☐

Did the child have any other problems in the first few days of life? ☐ Yes ☐ No
If yes, please explain: _____

_____

APPENDIX 4 – MEDICAL QUESTIONNAIRE FOR MALE SIBLINGS OF STUDY SUBJECTS

Medical Questionnaire for Male Siblings of Study Subjects

*One questionnaire to be completed by each male sibling

Participant's Initials: ☐☐☐

Participant's ID #: ☐☐☐
*To be completed by study personnel

Gender: ☐Male

Today's Date: ☐☐/☐☐/☐☐☐☐

Date of birth: ☐☐/☐☐/☐☐☐☐
DD/MM/YYYY

Are you currently experiencing any major medical problems that would prevent you from participating in this study? ☐Yes ☐No

Do you have a known hypersensitivity to pilocarpine or pilocarpine-like muscarinic agonists (Examples: Urecholine, Salagen, Pilocar, and Provocholine)? ☐Yes ☐No

Do you have a pacemaker? ☐Yes ☐No

Have you been diagnosed with HED? ☐Yes ☐No

If yes, age at diagnosis: ☐0-5 years ☐6-17 years ☐≥18 years

Do you have any family members diagnosed with HED? ☐Yes ☐No

If yes, check all that apply:
☐Mother
☐Father
☐Sisters
☐Brothers
☐Aunts
☐Uncles
☐Other

If other, specify:

Have you or any family member(s) had genetic testing for HED? ☐Yes ☐No

Do you know the genetic test results? ☐Yes ☐No

Have you ever been referred to any of the following types of physicians?

Dermatologist	☐Yes	☐No
Pediatric dermatologist	☐Yes	☐No
Geneticist	☐Yes	☐No
Genetic counselor	☐Yes	☐No
Dentist	☐Yes	☐No
Pediatric dentist	☐Yes	☐No

Do you have decreased sweating?	☐Yes ☐No
Do you sweat on certain parts of your body?	☐Yes ☐No
If so, from what body part(s) do you sweat and at what age did you notice you started sweating in that area?	
Body Part: ____________ Age you noticed:	☐0-5 yrs ☐11-17 yrs ☐6-10 yrs ☐≥18 yrs
Body Part: ____________ Age you noticed:	☐0-5 yrs ☐11-17 yrs ☐6-10 yrs ☐≥18 yrs
Body Part: ____________ Age you noticed:	☐0-5 yrs ☐11-17 yrs ☐6-10 yrs ☐≥18 yrs
Body Part: ____________ Age you noticed:	☐0-5 yrs ☐11-17 yrs ☐6-10 yrs ☐≥18 yrs
Body Part: ____________ Age you noticed:	☐0-5 yrs ☐11-17 yrs ☐6-10 yrs ☐≥18 yrs
Body Part: ____________ Age you noticed:	☐0-5 yrs ☐11-17 yrs ☐6-10 yrs ☐≥18 yrs
Do you have unexplained fevers?	☐Yes ☐No
Did you ever suffer from seizures associated with fever?	☐Yes ☐No
Do you suffer from heat intolerance?	☐Yes ☐No
Is your exercising limited by heat intolerance?	☐Yes ☐No

Does your decreased sweating/heat intolerance affect your: **Check all that apply*	☐Daily life ☐Choice of occupation ☐Involvement in indoor sports ☐Involvement in outdoor sports ☐Decision to live in cooler climate ☐Choice of vacation destinations ☐Ability to travel

Have you experienced hair or eyebrow thinning or scalp hair loss?	☐Yes ☐No
If yes, what age were you when you noticed the loss of hair?	☐0-5 yrs ☐6-10 yrs ☐11-17 yrs ☐≥18 yrs
How often do you get your hair cut?	☐Daily ☐Weekly ☐Monthly ☐Yearly
Do you get haircuts less often than unaffected siblings/ classmates?	☐Yes ☐No
Have you ever tried a topical treatment to reduce hair thinning?	☐Yes ☐No

Do you have problems with your teeth (no teeth, missing or misshapen teeth)?		☐ Yes	☐ No
If yes, describe age of treatment with dentures and/or implants if applicable (check all that apply):		Dentures	Implants
	1-5 years	☐	☐
	6-10 years	☐	☐
	11-17 years	☐	☐
	≥18 years	☐	☐
To the best of your knowledge how many baby teeth did you develop?		☐☐	
To the best of your knowledge how many adult teeth did you develop?		☐☐	
Do you suffer from dry mouth?		☐ Yes	☐ No
Do you suffer from dry eyes?		☐ Yes	☐ No
Do you require eye drops on a regular basis?		☐ Yes	☐ No
Do you suffer from frequent eye infections?		☐ Yes	☐ No

Did you have chronic nasal drainage/blockage as a child?		☐ Yes	☐ No
Did you suffer from nosebleeds as a child?		☐ Yes	☐ No
If yes, at what age did you first notice them?	☐ 0-5 yrs	☐ 11-17 yrs	
	☐ 6-10 yrs	☐ ≥18 yrs	
Do you still experience nosebleeds?		☐ Yes	☐ No
How many times per year do you have nosebleeds?	☐☐		
Did you have respiratory related problems as a child?		☐ Yes	☐ No
If yes, were you ever hospitalized for antibiotic therapy?		☐ Yes	☐ No
Do you suffer from sinus infections most years?		☐ Yes	☐ No
If so, at what age did these sinus infections start?	☐ 0-5 yrs	☐ 11-17 yrs	
	☐ 6-10 yrs	☐ ≥18 yrs	
Do you suffer from asthma?		☐ Yes	☐ No
If so, do you require medication to manage your asthma?		☐ Yes	☐ No
Do you experience a hoarseness of your voice?		☐ Yes	☐ No
If yes, at what age did you first notice it?		☐ Yes	☐ No
Is the hoarseness worse during the cold months?		☐ Yes	☐ No

Do you have problems with dry skin?	☐ Yes	☐ No
Have you ever had a diagnosis of eczema or atopic dermatitis?	☐ Yes	☐ No
If yes, have you tried prescription medications?	☐ Yes	☐ No

If yes, list medications:

Do you have a family history of eczema (other than XLHED males)? ☐Yes ☐No

Hypohidrosis Severity 5-Point Likert Scale

1	2	3	4	5
Sweat as much as people without ED	Sweat a little less than people without ED (no problems in hot weather)	Some problems in sweating (sometimes have problems in hot weather)	A little sweating (I have problems in hot weather	No sweating at all (I have problems in hot weather)

Alopecia (hair loss or thinning) Severity 5-Point Likert Scale

1	2	3	4	5
Normal hair	Mild (<25%) hair loss	Moderate (25-75%) hair loss	Severe (>75%) hair loss	No hair

APPENDIX 5 – OCULAR SURFACE DISEASE INDEX© (OSDI©)

Provided as a separate document.

REFERENCES

Black, MM, Matula K. 2000. *Essentials of Bayley Scales of Infant Development-II Assessment*. New York, J Wiley & Sons, Inc.

Blüschke G, Nusken KD, Schneider H. 2010. Prevalence and prevention of severe complications of hypohidrotic ectodermal dysplasia in infancy. *Am J Med Gen A*. 86: 397-9.

Casal M, Lewis J, Mauldin E, Tardivel A, Ingold K, Favre M, Paradies F, Demotz S, Gaide O, Schneider P. 2007. Significant Correction of Disease after Postnatal Administration of Recombinant Ectodysplasin A in Canine X-Linked Ectodermal Dysplasia. *Am J Hum Genet*. 81: 1050-1056.

Chawla, D, Agarwal R, Deorari A, Paul, V. 2008. Fluid and electrolyte management in term and preterm neonates. NICU Protocol. Division of Neonatology, Department of Pediatrics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi.

Clarke A, Sarfarazi M, Thomas NS, Roberts K, Harper PS. 1987. X-linked hypohidrotic ectodermal dysplasia: DNA probe linkage analysis and gene localization. *Hum Genet.* 75(4): 378-80.

Cloherty JP, Eichenwald EC, Stark AR. 2004. Manual of Neonatal Care (Fifth Ed). Philadelphia, PA: Lippincott, Williams & Wilkins.

Cluzeau C, Hadj-Rabia S, Bal E, Clauss F, Munnich A, Bodemer C, Headon D, Smahi A. 2012. The EDAR370A allele attenuates the severity of hypohidrotic ectodermal dysplasia caused by EDA gene mutation. *Br J Dermatol* 166:678-81.

Dietz J, Kaercher T, Schneider AT, Zimmerman T, Huttner K, Johnson R, Schneider H. 2013 Apr 4. Early respiratory and ocular involvement in X-linked hypohidrotic ectodermal dysplasia. *Eur J Pediatr* Epub ahead of print.

Ectodysplasin A (Fc:EDA1 aka EDI200) Replacement Therapy In A Canine Model Of Ectodermal Dysplasia: Pharmacological Assessment (NCD-200-11-005). Edimer Pharmaceuticals, Inc.

EDI200: A 3-Week Intraperitoneal/Intravenous Toxicity Study in Juvenile Dogs with a 2-Week Recovery Period (1800-010). Edimer Pharmaceuticals, Inc.

EDI200: A 3-Week Intraperitoneal Toxicity Study in Juvenile Mice with a 2-Week Recovery Period (1800-009). Edimer Pharmaceuticals, Inc.

"Electronic Records: Electronic Signatures." *Code of Federal Regulations* Title 21, Pt. 11, 2011 ed.

Gaide O, Schneider P. 2003. Permanent Correction of an Inherited Ectodermal Dysplasia with Recombinant EDA. *Nat Med*. 9: 614-618.

Haycock, G. B., Schwartz, G. J., & Wisotsky, D. H. 1978. Geometric method for measuring body surface area: a height-weight formula validated in infants, children, and adults. *J Pediatr*. 93(1), 62-6.

Hey E. 1975. Thermal neutrality. *British Med Bull*. *31*(1): 69-74.

Huttner K, Grange D, Klein O, Schneider H. 2012, February. Genotype/phenotype correlations in XLHED: Insights into the biology of ectodysplasin. Poster session presented at the 2012 Dermatogenetics Conference. Miami, Florida.

Itoh H, Uebori S, Asai M, Kashiwaya T, Atoh K, Makino I. 2003. Early Detection of Orthostatic Hypotension by Quantitative Sudomotor Axon Reflex Test (QSART) in Type 2 Diabetic Patients. *Internal Med*. 42: 560-564.

Low P, Caskey P, Tuck R, Fealey R, Dyck P. 1983. Quantitative Sudomotor Axon Reflex Test in Normal and Neuropathic Subjects. *Ann Neurol*. 14: 573-580.

Mastella G, Di Cesare G, Borruso A, Menin L, Zanolla L. 2000. Reliability of sweat testing by the Macroduct collection method combined with conductivity analysis in comparison with the classic Gibson and Cooke technique. *Acta Paediatrica. 89*(8): 933-7.

Mauldin E, Gaide O, Schneider P, Casal M. 2009. Neonatal Treatment with Recombinant Ectodysplasin Prevents Respiratory Disease in Dogs with X-Linked Ectodermal Dysplasia. *Am J Med Genet A.* 149A: 2045-2049.

Miller, R. 2003. Marginal Transfer of ReoPro™ (Abciximab) Compared with Immunoglobulin G (F105), Inulin and Water in the Perfused Human Placenta In Vitro. *Placenta*. *24*(7): 727-738.

Motil KJ, Fete TJ, Fraley JK, Schultz RJ, Foy TM, Ochs U, et al. 2005. Growth Characteristics Of Children With Ectodermal Dysplasia Syndromes. *Pediatrics*. 116(2): 229-34.

Ramaswami U, Wendt S, Pintos-Morell G, Parini R, Whybra C, Leon Leal J, Santus F, Beck M. 2007. Enzyme Replacement Therapy with Agalsidase Alfa in Children with Fabry Disease. *Acta Paediatr*. 96: 122-127.

Rutter N, Hull D. 1979. Response of term babies to a warm environment. *Arch Dis Child. 54*(3): 178-183.

Seeliger F, Drögemüller C, Tegtmeier P, Baumgärtner W, Distl O, & Leeb T. 2005. Ectodysplasin-1 deficiency in a German Holstein bull associated with loss of respiratory mucous glands and chronic rhinotracheitis. *J Comp Pathol*. 132(4): 346-9.

Sjörs G, Hammarlund K, Sedin, G. 1997. Thermal balance in term and preterm newborn infants nursed in an incubator equipped with a radiant heat source. *Acta Paediatrica. 86*(4): 403-9.

Stothers J K, Warner R M. 1984. Thermal balance and sleep state in the newborn. *Early Hum Dev*. *9*(4): 313-22.

Sulyok E, Jequier E, Prod'hom L. 1976. Relationship between body size, thermal balance and thermal insulation of term infants under various ambient conditions. *Biol Neonate*. *28*: 42-56.

Sweat Duct Imaging in Mother/Newborn Dyads (ECP-005). Clinical Study Report. Edimer Pharmaceuticals, Inc.

Swischuk, L. 2003. Imaging of the Newborn, Infant and Young Child (Fifth). Philadelphia, PA: Lippincott, Williams and Wilkins.

The Effect of Ectodysplasin A (Fc: EDA1) Replacement Therapy in a Canine Model of Ectodermal Dysplasia (NCD-22-11-004). Edimer Pharmaceuticals, Inc.

Ulm M R, Kratochwil A, Ulm B, Solar P, Aro G, Bernaschek, G. 1998. Three-dimensional ultrasound evaluation of fetal tooth germs. *Ultrasound Obst Gyn*. *12*(4): 240-3.

Zankl A, Addor M, Cousin P, Gaide A, Gudinchet F, Schorderet D. 2001. Fatal outcome in a female monozygotic twin with X-linked hypohidrotic ectodermal dysplasia (XLHED) due to a de novo t(X;9) translocation with probable disruption of the EDA gene. *Eur J Pediatr*. 160: 296-99.

Appendix 16.1.2- Sample Case Report Forms

Sample Case Report Form
11 SEP 2015

Site | Visit Name: SCREENING | Not Done ☐

Subject | Patient Initials

DEMOGRAPHICS, CONSENT, AND ELIGIBILITY

Maternal Screening ICF dd-mmm-yyyy

Interventional Study Minor ICF dd-mmm-yyyy

Date of Birth dd-mmm-yyyy

Gender

☐ Male ☐ Female

Ethnicity

☐ **Hispanic or Latino**

☐ **Not Hispanic or Latino**

Race *(check all that apply)*

☐ **American Indian / Alaska Native**

☐ **Asian**

☐ **Black / African American**

☐ **Native Hawaiian / Pacific Islander**

☐ **White**

PROTOCOL VERSION

Under what Protocol Version was the subject enrolled?

☐ **Protocol Version 3 Date 24JUN2013**

☐ **Amendment** **Version** **Dated**

INCLUSION/EXCLUSION CRITERIA

Does the subject meet eligibility requirements? ☐ **Yes** ☐ **No**

If no, indicate criteria which was not met:

Inclusion / Exclusion	Criteria Number	Specify Deviation	Waiver Granted? Yes	No
☐ I ☐ E			☐	☐
☐ I ☐ E			☐	☐
☐ I ☐ E			☐	☐

Genetic Testing

Genetic Testing for XLHED

Date of genetic diagnosis:
dd-mmm-yyyy

Name of laboratory performing testing (free text)

Result of genetic testing (free text)

Test was conducted ☐ Antenatally ☐ Postnatally

MEDICAL HISTORY

Has the subject had any medical conditions and/or procedures? ☐ Yes ☐ No

Description of Condition or Procedure (record one per line)	Currently Active	Year of Onset	Date of Resolution
	☐ Yes ☐ No		
	☐ Yes ☐ No		
	☐ Yes ☐ No		
	☐ Yes ☐ No		
	☐ Yes ☐ No		
	☐ Yes ☐ No		
	☐ Yes ☐ No		
	☐ Yes ☐ No		
	☐ Yes ☐ No		
	☐ Yes ☐ No		
	☐ Yes ☐ No		
	☐ Yes ☐ No		
	☐ Yes ☐ No		
	☐ Yes ☐ No		
	☐ Yes ☐ No		

Site		Visit Name	SCREENING	Not Done	
Subject		Patient Initials			

MEDICAL QUESTIONNAIRE - MOTHERS AND XLHED-AFFECTED NEONATES

Todays Date:

Has the mother been diagnosed with HED? ☐ Yes ☐ No

If yes, age at diagnosis: ☐ 0-5 years ☐ 6-17 years ☐ >=18 years

Do you have any family members diagnosed with HED? ☐ Yes ☐ No

If yes, check all that apply:
- ☐ Mother
- ☐ Father
- ☐ Sisters
- ☐ Brothers
- ☐ Aunts
- ☐ Uncles
- ☐ Other, specify below:

Has the mother or any family member(s) had genetic testing for HED? ☐ Yes ☐ No

Mother's age at delivery:

What number pregnancy is/was this child for the mother?

Is the mother currently pregnant? ☐ Yes ☐ No

Thinking of all of the mother's pregnancies to date, including this one, how many resulted in each of the following:

- Miscarriage in the first trimester (up to the 14th week of pregnancy)
- Miscarriage later in pregnancy
- Stillbirth
- Preterm birth (prior to 37 weeks)
- Full term birth (37 weeks or more)

Did the mother have any of the following complications during the child's (the study subject) pregnancy? ☐ Yes ☐ No

If yes, please list treatment:

- Diabetes:
- High blood pressure:
- Infections, fevers and illnesses:
- Other problems/complications:
- Medications used during pregnancy:

Site		Visit Name	SCREENING	Not Done	
Subject		Patient Initials			

MEDICAL QUESTIONNAIRE - MOTHERS AND XLHED-AFFECTED NEONATES (CONTINUED)

Are any of these medications investigational: ☐ Yes ☐ No

Did the mother have any of the following?
- ☐ Ultrasound
- ☐ 1st trimester screen/triple.quad screen
- ☐ Amniocentesis or CVS

Were any results from this testing abnormal? ☐ Yes ☐ No

If yes, please explain:

The child was born: ☐ Full-term ☐ Prematurely ____ Weeks Premature

If premature, please list the reason:

The child was born: ☐ Vaginally ☐ By C-section

If by C-section, why:

Birth Hospital:

City:

State, if applicable:

Country:

Birth Weight: ____ **kg**

Birth Length: ____ **cm**

Birth Head Circumference: ____ **cm**

Did your child have any problems after delivery or require admission to the Neonatal Intensive Care Unit (NICU)? ☐ Yes ☐ No

If yes, please explain:

Did he pass the newborn screen: ☐ Yes ☐ No ☐ Unsure

If no, what part(s) did he not pass:

How many days old was child when he went home from the hospital? ____ ☐ Not yet gone home

If not yet gone home, please explain:

Did the child have any other problems in the first few days of life? ☐ Yes ☐ No

If yes, please explain:

Site		Visit Name	BASELINE	Not Done	
Patient		Patient Initials		Visit Date	

CHEMISTRY

Sample Date: **dd-mmm-yyyy** **Time:** **hh:mm** **(24-hour clock)**

Lab Name:

			Reference Ranges			If Abnormal	
Assay	**Result**	**Unit**	**Low**	**High**	**Flag**	**CS**	**NCS**
Sodium (Na)						☐	☐
Potassium (K)						☐	☐
Chloride						☐	☐
Calcium						☐	☐
BUN						☐	☐
Glucose						☐	☐
Creatinine						☐	☐
Total Protein						☐	☐
Albumin						☐	☐
AST (SGOT)						☐	☐
ALT (SGPT)						☐	☐
Alkaline Phosphatase						☐	☐

***CS - clinically significant, NCS - not clinically significant**

If any of these results are clinically significant (CS) at Baseline, list condition on the medical history page. If any of these results are clinically significant (CS) for Visits TD 1, 15, 21 and Mon 2 & 6 of Life, list condition on the Adverse Events page.

HEMATOLOGY

Sample Date: dd-mmm-yyyy **Time:** hh:mm

Lab Name

			Reference Ranges			If Abnormal	
	Result	**Unit**	**Low**	**High**	**Flag**	**CS**	**NCS**
WBC						☐	☐
RBC						☐	☐
Hemoglobin						☐	☐
Hematocrit						☐	☐
Platelets						☐	☐
Neutrophils						☐	☐
Lymphocytes						☐	☐
Monocytes						☐	☐
Eosinophils						☐	☐
Basophils						☐	☐

CS - clinically significant, NCS - not clinically significant

*If any of these results are clinically significant (CS) at Baseline, list condition on the Medical History page. If any of these results are clinically significant (CS) for Visits TD 1, 15, 21 and Mon 2 & 6 of Life, , list condition on the Adverse Events page.

Site		Visit Name	BASELINE	Not Done	
Subject		Patient Initials		Visit Date	

URINALYSIS

Sample Date: _____ (dd-mmm-yyyy) **Time:** _____ (hh:mm) **Lab ID:** _____

Urine Parameter	Result	If Abnormal CS	If Abnormal NCS
Specific Gravity		☐	☐
pH		☐	☐

Component	Result	If Abnormal CS	If Abnormal NCS
Protein		☐	☐
Glucose		☐	☐
Ketones		☐	☐
Nitrite		☐	☐
Bilirubin		☐	☐
Blood		☐	☐
Leucocytes		☐	☐
Urobilinogen		☐	☐

Microscopic *(refer to completion guidelines)*

Component	Result	If Abnormal CS	If Abnormal NCS
WBC		☐	☐
RBC		☐	☐
Epithelial Cells		☐	☐
Bacteria		☐	☐
Casts		☐	☐
Crystals		☐	☐
Mucus		☐	☐

If any of these results are clinically significant (CS) as Baseline, list condition on the medical history page. If any of these results are clinically significant (CS) for Visits TD 1, 15, 21 and Mon 2 & 6 of Lief, list condition on the Adverse Events page.

PK SAMPLING - Neonate

Date of PK Sampling	**Sampling Time**
dd-mmm-yyyy	24-hour clock

Blood Sample Collection Date: dd-mmm-yyyy

Accession Number:

Genetic Testing for Polymorphism EDAR V370A

EDAR genotyping for phenotype-modifying polymorphism EDAR V370A

Date of genetic testing:
dd-mmm-yyyy

Name of laboratory performing testing (free text)

Result of genetic testing (free text)

Site		Visit Name	BASELINE	Not Done	
Subject		Patient Initials		Visit Date	

PHYSICAL EXAM - FULL - Neonate

Date of Physical Exam: _____
dd-mmm-yyyy

Length: _____ ☐ CM ☐ IN **Weight:** _____ ☐ KG ☐ LB
Head Circumfrence: _____ ☐ CM ☐ IN

Vital Signs:
1. Temperature: _____ ☐ C ☐ F **2. Respiration Rate:** _____ Breaths per minute
3. Blood Pressure: _____ _____ mmHg **4. Heart Rate:** _____ Beats per minute
Systolic / Diastolic

Body System	Normal	Abnormal	Not Evaluated	If Abnormal, specify findings
Head	☐	☐	☐	
Ears	☐	☐	☐	
Eyes	☐	☐	☐	
Mouth	☐	☐	☐	
Skin Appearance	☐	☐	☐	
Cardiovascular	☐	☐	☐	
Pulmonary	☐	☐	☐	
Abdomen	☐	☐	☐	
Hips and Legs	☐	☐	☐	
Genitalia	☐	☐	☐	

Growth and Development - Developmental Status:

Date:
dd-mmm-yyyy:

Devlopmental Status for Gestational Age ☐ Normal ☐ Abnormal ☐ Not Applicable

If abnormal, explain (free text):

Growth and Development - Feeding

Date:
dd-mmm-yyyy:

Feeding ☐ Normal ☐ Abnormal

If abnormal, explain (free text):

FACIAL DEVELOPMENT

Date of Facial Photographs

dd-mmm-yyyy

Photograph View

- ☐ Frontal
- ☐ Lateral
- ☐ Both Frontal and Lateral

If Lateral, select side

- ☐ Right
- ☐ Left
- ☐ Both Right and Left

DENTAL IMAGING

Date of Imaging: _____
dd-mmm-yyyy

Were Tooth Buds present? ☐ Yes ☐ No

Number of Tooth Buds _____

Dry Eye Assessment:

Date of Assessment:
dd-mmm-yyyy

Exam	Select Result for Left Eye from Drop Down List	Select Result for Right Eye from Drop Down List
Corneal Exam		

Exam	Select Result for Left Eye from Drop Down List	Select Result for Right Eye from Drop Down List
Eyelid Exam for Melbomian Gland Openings		

Was Non-Invasive Break Up Time (NIBUT) assessed? ☐ Yes ☐ No ☐ Unable to assess

NIBUT Results

Right Eye ____ sec Left Eye ____ sec

Other findings, please comment:

THERMOREGULATION VITAL SIGNS - Neonate

Select Time Point from Drop-Down List	**Date of Vitals** dd-mmm-yyyy	**Time of Vitals** hh:mm	**Humidity**	**Incubator Temperature** C F	**Subject Temperature** C F	**Heart Rate** (beats/min)	**Respiration Rate** (breaths/min)
			%				
			%				
			%				
			%				
			%				
			%				
			%				
			%				
			%				
			%				

Report any clinical significant changes that are a clinical worsening of baseline on the Adverse Events page.

Site		Visit Name	BASELINE	Not Done	
Subject		Patient Initials		Visit Date	

SWEAT RATE - Neonate Sibling

Date of Assessment

dd-mmm-yyyy

SWEAT RATE

Assay	Result	Unit	Start Time hh:mm	End Time hh:mm
Sweat Volume*		uL		

The macroduct sweat collector is held in place for approximately 30 minutes. See protocol for futher instructions.

SWEAT DUCT DENSITY

Date of Assessment:

dd-mmm-yyyy

BIOPSY - Neonate

BIOPSY

Date of Biopsy	**Time of Biopsy**	**Leg Biopsied**
dd-mmm-yyyy	(24HR CLOCK)	☐ Left ☐ Right

Site		Visit Name	TD 0	Not Done	
Subject		Patient Initials		Visit Date	

PHYSICAL EXAM - BRIEF - Neonate

Date of Physical Exam: _____
dd-mmm-yyyy

Weight: _____ ☐ KG ☐ LB

Vital Signs:

1. Temperature: _____ ☐ C ☐ F

2. Respiration Rate: _____ Breaths per minute

3. Blood Pressure: _____ _____ mmHg
Systolic / Diastolic

4. Heart Rate: _____ Beats per minute

Body System	Normal	Abnormal	Not Evaluated	If Abnormal, specify findings
General Appearance	☐	☐	☐	
Skin Appearance	☐	☐	☐	
Cardiovascular	☐	☐	☐	
Pulmonary	☐	☐	☐	
Abdominal	☐	☐	☐	

Site		Visit Name	TD 0	Not Done	
Subject		Patient Initials		Visit Date	

PK SAMPLING - Neonate

Time Point	Date of PK Sampling dd-mmm-yyyy	Sampling Time 24-hour clock
15 Minutes Post Dose		
3 Hours Post Dose		
8 Hours Post Dose		
24 Hours Post Dose		
48 Hours Post Dose		

DOSING VITALS - Neonate

Date of Vitals:
dd-mmm-yyyy:

Time Point	Date of Vitals dd-mmm-yyyy	Time of Vitals hh:mm	Blood Pressure (mmHg) Systolic	Blood Pressure (mmHg) Diastolic	Heart Rate (beats/min)	Respiration Rate (breaths/min)	Temperature			Select Method used to obtain Temperature from Drop Down List	If Other, Specify
Pre-dose								☐ C	☐ F		
15 minutes Post Dose								☐ C	☐ F		
1 Hour Post Dose								☐ C	☐ F		
4 Hours Post Dose								☐ C	☐ F		
8 Hours Post Dose								☐ C	☐ F		
12 Hours Post Dose								☐ C	☐ F		
16 Hours Post Dose								☐ C	☐ F		
20 Hours Post Dose								☐ C	☐ F		
24 Hours Post Dose								☐ C	☐ F		

***For Day 0, Pre-Dose, report any results that are clinically significant (CS) on the Medical History page. For all other collection times, report any results that are clinically significant on the Adverse Events page.**

Site		Visit Name	TD 1	Not Done	
Subject		Patient Initials		Visit Date	

PHYSICAL EXAM - BRIEF - Neonate

Date of Physical Exam: _____
dd-mmm-yyyy

Weight: _____ ☐ KG ☐ LB

Vital Signs:

1. Temperature: _____ ☐ C ☐ F

2. Respiration Rate: _____ Breaths per minute

3. Blood Pressure: _____ _____ mmHg
Systolic / Diastolic

4. Heart Rate: _____ Beats per minute

Body System	Normal	Abnormal	Not Evaluated	If Abnormal, specify findings
General Appearance	☐	☐	☐	
Skin Appearance	☐	☐	☐	
Cardiovascular	☐	☐	☐	
Pulmonary	☐	☐	☐	
Abdominal	☐	☐	☐	

Site		Visit Name	TD 1	Not Done	
Patient		Patient Initials		Visit Date	

CHEMISTRY

Sample Date: **dd-mmm-yyyy** **Time:** **hh:mm** **(24-hour clock)**

Lab Name:

			Reference Ranges			If Abnormal	
Assay	**Result**	**Unit**	**Low**	**High**	**Flag**	**CS**	**NCS**
Sodium (Na)						☐	☐
Potassium (K)						☐	☐
Chloride						☐	☐
Calcium						☐	☐
BUN						☐	☐
Glucose						☐	☐
Creatinine						☐	☐
Total Protein						☐	☐
Albumin						☐	☐
AST (SGOT)						☐	☐
ALT (SGPT)						☐	☐
Alkaline Phosphatase						☐	☐

***CS - clinically significant, NCS - not clinically significant**

If any of these results are clinically significant (CS) at Baseline, list condition on the medical history page. If any of these results are clinically significant (CS) for Visits TD 1, 15, 21 and Mon 2 & 6 of Life, list condition on the Adverse Events page.

HEMATOLOGY

Sample Date: dd-mmm-yyyy **Time:** hh:mm

Lab Name

			Reference Ranges			If Abnormal	
	Result	**Unit**	**Low**	**High**	**Flag**	**CS**	**NCS**
WBC						☐	☐
RBC						☐	☐
Hemoglobin						☐	☐
Hematocrit						☐	☐
Platelets						☐	☐
Neutrophils						☐	☐
Lymphocytes						☐	☐
Monocytes						☐	☐
Eosinophils						☐	☐
Basophils						☐	☐

CS - clinically significant, NCS - not clinically significant

*If any of these results are clinically significant (CS) at Baseline, list condition on the Medical History page. If any of these results are clinically significant (CS) for Visits TD 1, 15, 21 and Mon 2 & 6 of Life, , list condition on the Adverse Events page.

Site		Visit Name	TD 1	Not Done	
Subject		Patient Initials		Visit Date	

URINALYSIS

Sample Date: _____ (dd-mmm-yyyy) **Time:** _____ (hh:mm) **Lab ID:** _____

Urine Parameter	Result	If Abnormal CS	If Abnormal NCS
Specific Gravity		☐	☐
pH		☐	☐

Component	Result	If Abnormal CS	If Abnormal NCS
Protein		☐	☐
Glucose		☐	☐
Ketones		☐	☐
Nitrite		☐	☐
Bilirubin		☐	☐
Blood		☐	☐
Leucocytes		☐	☐
Urobilinogen		☐	☐

Microscopic *(refer to completion guidelines)*

Component	Result	If Abnormal CS	If Abnormal NCS
WBC		☐	☐
RBC		☐	☐
Epithelial Cells		☐	☐
Bacteria		☐	☐
Casts		☐	☐
Crystals		☐	☐
Mucus		☐	☐

If any of these results are clinically significant (CS) as Baseline, list condition on the medical history page. If any of these results are clinically significant (CS) for Visits TD 1, 15, 21 and Mon 2 & 6 of Lief, list condition on the Adverse Events page.

BIOPSY - Neonate

BIOPSY

Date of Biopsy	**Time of Biopsy**	**Leg Biopsied**
dd-mmm-yyyy	(24HR CLOCK)	☐ Left ☐ Right

Site		Visit Name	TD 4	Not Done	
Subject		Patient Initials		Visit Date	

PHYSICAL EXAM - BRIEF - Neonate

Date of Physical Exam: _____
dd-mmm-yyyy

Weight: _____ ☐ KG ☐ LB

Vital Signs:

1. Temperature: _____ ☐ C ☐ F

2. Respiration Rate: _____ Breaths per minute

3. Blood Pressure: _____ _____ mmHg
Systolic / Diastolic

4. Heart Rate: _____ Beats per minute

Body System	Normal	Abnormal	Not Evaluated	If Abnormal, specify findings
General Appearance	☐	☐	☐	
Skin Appearance	☐	☐	☐	
Cardiovascular	☐	☐	☐	
Pulmonary	☐	☐	☐	
Abdominal	☐	☐	☐	

DOSING VITALS - Neonate

Date of Vitals:
dd-mmm-yyyy:

Time Point	Date of Vitals dd-mmm-yyyy	Time of Vitals hh:mm	Blood Pressure (mmHg) Systolic	Blood Pressure (mmHg) Diastolic	Heart Rate (beats/min)	Respiration Rate (breaths/min)	Temperature			Select Method used to obtain Temperature from Drop Down List	If Other, Specify
Pre-dose								☐ C	☐ F		
15 minutes Post Dose								☐ C	☐ F		
1 Hour Post Dose								☐ C	☐ F		
4 Hours Post Dose								☐ C	☐ F		
8 Hours Post Dose								☐ C	☐ F		
12 Hours Post Dose								☐ C	☐ F		
16 Hours Post Dose								☐ C	☐ F		
20 Hours Post Dose								☐ C	☐ F		
24 Hours Post Dose								☐ C	☐ F		

***For Day 0, Pre-Dose, report any results that are clinically significant (CS) on the Medical History page. For all other collection times, report any results that are clinically significant on the Adverse Events page.**

Site		Visit Name	TD 7	Not Done	
Subject		Patient Initials		Visit Date	

PHYSICAL EXAM - BRIEF - Neonate

Date of Physical Exam: _____
dd-mmm-yyyy

Weight: _____ ☐ KG ☐ LB

Vital Signs:

1. Temperature: _____ ☐ C ☐ F

2. Respiration Rate: _____ Breaths per minute

3. Blood Pressure: _____ _____ mmHg
Systolic / Diastolic

4. Heart Rate: _____ Beats per minute

Body System	Normal	Abnormal	Not Evaluated	If Abnormal, specify findings
General Appearance	☐	☐	☐	
Skin Appearance	☐	☐	☐	
Cardiovascular	☐	☐	☐	
Pulmonary	☐	☐	☐	
Abdominal	☐	☐	☐	

DOSING VITALS - Neonate

Date of Vitals:
dd-mmm-yyyy:

Time Point	Date of Vitals dd-mmm-yyyy	Time of Vitals hh:mm	Blood Pressure (mmHg) Systolic	Blood Pressure (mmHg) Diastolic	Heart Rate (beats/min)	Respiration Rate (breaths/min)	Temperature			Select Method used to obtain Temperature from Drop Down List	If Other, Specify
Pre-dose								☐ C	☐ F		
15 minutes Post Dose								☐ C	☐ F		
1 Hour Post Dose								☐ C	☐ F		
4 Hours Post Dose								☐ C	☐ F		
8 Hours Post Dose								☐ C	☐ F		
12 Hours Post Dose								☐ C	☐ F		
16 Hours Post Dose								☐ C	☐ F		
20 Hours Post Dose								☐ C	☐ F		
24 Hours Post Dose								☐ C	☐ F		

***For Day 0, Pre-Dose, report any results that are clinically significant (CS) on the Medical History page. For all other collection times, report any results that are clinically significant on the Adverse Events page.**

Site		Visit Name	TD 11	Not Done	
Subject		Patient Initials		Visit Date	

PHYSICAL EXAM - BRIEF - Neonate

Date of Physical Exam: _____
dd-mmm-yyyy

Weight: _____ ☐ KG ☐ LB

Vital Signs:

1. Temperature: _____ ☐ C ☐ F

2. Respiration Rate: _____ Breaths per minute

3. Blood Pressure: _____ _____ mmHg
Systolic / Diastolic

4. Heart Rate: _____ Beats per minute

Body System	Normal	Abnormal	Not Evaluated	If Abnormal, specify findings
General Appearance	☐	☐	☐	
Skin Appearance	☐	☐	☐	
Cardiovascular	☐	☐	☐	
Pulmonary	☐	☐	☐	
Abdominal	☐	☐	☐	

DOSING VITALS - Neonate

Date of Vitals:
dd-mmm-yyyy:

Time Point	Date of Vitals dd-mmm-yyyy	Time of Vitals hh:mm	Blood Pressure (mmHg) Systolic	Blood Pressure (mmHg) Diastolic	Heart Rate (beats/min)	Respiration Rate (breaths/min)	Temperature			Select Method used to obtain Temperature from Drop Down List	If Other, Specify
Pre-dose								☐ C	☐ F		
15 minutes Post Dose								☐ C	☐ F		
1 Hour Post Dose								☐ C	☐ F		
4 Hours Post Dose								☐ C	☐ F		
8 Hours Post Dose								☐ C	☐ F		
12 Hours Post Dose								☐ C	☐ F		
16 Hours Post Dose								☐ C	☐ F		
20 Hours Post Dose								☐ C	☐ F		
24 Hours Post Dose								☐ C	☐ F		

***For Day 0, Pre-Dose, report any results that are clinically significant (CS) on the Medical History page. For all other collection times, report any results that are clinically significant on the Adverse Events page.**

Site		Visit Name	TD 14	Not Done	
Subject		Patient Initials		Visit Date	

PHYSICAL EXAM - BRIEF - Neonate

Date of Physical Exam: dd-mmm-yyyy

Weight: ☐ ☐ KG ☐ LB

Vital Signs:

1. Temperature: ☐ ☐ C ☐ F

2. Respiration Rate: ☐ Breaths per minute

3. Blood Pressure: ☐ ☐ mmHg
Systolic / Diastolic

4. Heart Rate: ☐ Beats per minute

Body System	Normal	Abnormal	Not Evaluated	If Abnormal, specify findings
General Appearance	☐	☐	☐	
Skin Appearance	☐	☐	☐	
Cardiovascular	☐	☐	☐	
Pulmonary	☐	☐	☐	
Abdominal	☐	☐	☐	

DOSING VITALS - Neonate

Date of Vitals:
dd-mmm-yyyy:

Time Point	Date of Vitals dd-mmm-yyyy	Time of Vitals hh:mm	Blood Pressure (mmHg) Systolic	Blood Pressure (mmHg) Diastolic	Heart Rate (beats/min)	Respiration Rate (breaths/min)	Temperature			Select Method used to obtain Temperature from Drop Down List	If Other, Specify
Pre-dose								☐ C	☐ F		
15 minutes Post Dose								☐ C	☐ F		
1 Hour Post Dose								☐ C	☐ F		
4 Hours Post Dose								☐ C	☐ F		
8 Hours Post Dose								☐ C	☐ F		
12 Hours Post Dose								☐ C	☐ F		
16 Hours Post Dose								☐ C	☐ F		
20 Hours Post Dose								☐ C	☐ F		
24 Hours Post Dose								☐ C	☐ F		

***For Day 0, Pre-Dose, report any results that are clinically significant (CS) on the Medical History page. For all other collection times, report any results that are clinically significant on the Adverse Events page.**

Site		Visit Name	TD 14	Not Done	
Subject		Patient Initials		Visit Date	

PK SAMPLING - Neonate

Time Point	Date of PK Sampling dd-mmm-yyyy	Sampling Time 24-hour clock
Pre-dose		
15 Minutes Post Dose		
3 Hours Post Dose		
18 Hours Post Dose		
48 Hours Post Dose		
168 Hours Post Dose		

Site		Visit Name	TD 15	Not Done	
Subject		Patient Initials		Visit Date	

PHYSICAL EXAM - BRIEF - Neonate

Date of Physical Exam: _____
dd-mmm-yyyy

Weight: _____ ☐ KG ☐ LB

Vital Signs:

1. Temperature: _____ ☐ C ☐ F

2. Respiration Rate: _____ Breaths per minute

3. Blood Pressure: _____ _____ mmHg
Systolic / Diastolic

4. Heart Rate: _____ Beats per minute

Body System	Normal	Abnormal	Not Evaluated	If Abnormal, specify findings
General Appearance	☐	☐	☐	
Skin Appearance	☐	☐	☐	
Cardiovascular	☐	☐	☐	
Pulmonary	☐	☐	☐	
Abdominal	☐	☐	☐	

BIOPSY - Neonate

BIOPSY

Date of Biopsy	**Time of Biopsy**	**Leg Biopsied**
		☐ Left ☐ Right
dd-mmm-yyyy	(24HR CLOCK)	

CHEMISTRY

Sample Date: **dd-mmm-yyyy** **Time:** **hh:mm** **(24-hour clock)**

Lab Name:

			Reference Ranges			If Abnormal	
Assay	**Result**	**Unit**	**Low**	**High**	**Flag**	**CS**	**NCS**
Sodium (Na)						☐	☐
Potassium (K)						☐	☐
Chloride						☐	☐
Calcium						☐	☐
BUN						☐	☐
Glucose						☐	☐
Creatinine						☐	☐
Total Protein						☐	☐
Albumin						☐	☐
AST (SGOT)						☐	☐
ALT (SGPT)						☐	☐
Alkaline Phosphatase						☐	☐

***CS - clinically significant, NCS - not clinically significant**

If any of these results are clinically significant (CS) at Baseline, list condition on the medical history page. If any of these results are clinically significant (CS) for Visits TD 1, 15, 21 and Mon 2 & 6 of Life, list condition on the Adverse Events page.

HEMATOLOGY

Sample Date: dd-mmm-yyyy **Time:** hh:mm

Lab Name

			Reference Ranges			If Abnormal	
	Result	**Unit**	**Low**	**High**	**Flag**	**CS**	**NCS**
WBC						☐	☐
RBC						☐	☐
Hemoglobin						☐	☐
Hematocrit						☐	☐
Platelets						☐	☐
Neutrophils						☐	☐
Lymphocytes						☐	☐
Monocytes						☐	☐
Eosinophils						☐	☐
Basophils						☐	☐

CS - clinically significant, NCS - not clinically significant

*If any of these results are clinically significant (CS) at Baseline, list condition on the Medical History page. If any of these results are clinically significant (CS) for Visits TD 1, 15, 21 and Mon 2 & 6 of Life, , list condition on the Adverse Events page.

Site		Visit Name	TD 16	Not Done	
Subject		Patient Initials		Visit Date	

URINALYSIS

Sample Date: _____ (dd-mmm-yyyy) **Time:** _____ (hh:mm) **Lab ID:** _____

Urine Parameter	Result	If Abnormal CS	If Abnormal NCS
Specific Gravity		☐	☐
pH		☐	☐

Component	Result	If Abnormal CS	If Abnormal NCS
Protein		☐	☐
Glucose		☐	☐
Ketones		☐	☐
Nitrite		☐	☐
Bilirubin		☐	☐
Blood		☐	☐
Leucocytes		☐	☐
Urobilinogen		☐	☐

Microscopic *(refer to completion guidelines)*

Component	Result	If Abnormal CS	If Abnormal NCS
WBC		☐	☐
RBC		☐	☐
Epithelial Cells		☐	☐
Bacteria		☐	☐
Casts		☐	☐
Crystals		☐	☐
Mucus		☐	☐

If any of these results are clinically significant (CS) as Baseline, list condition on the medical history page. If any of these results are clinically significant (CS) for Visits TD 1, 15, 21 and Mon 2 & 6 of Lief, list condition on the Adverse Events page.

Blood Sample Collection Date: dd-mmm-yyyy

Accession Number:

Site		Visit Name	TD 21	Not Done	
Subject		Patient Initials		Visit Date	

PHYSICAL EXAM - FULL - Neonate

Date of Physical Exam: _____
dd-mmm-yyyy

Length: _____ ☐ CM ☐ IN **Weight:** _____ ☐ KG ☐ LB
Head Circumfrence: _____ ☐ CM ☐ IN

Vital Signs:
1. Temperature: _____ ☐ C ☐ F **2. Respiration Rate:** _____ Breaths per minute
3. Blood Pressure: _____ _____ mmHg **4. Heart Rate:** _____ Beats per minute
Systolic / Diastolic

Body System	Normal	Abnormal	Not Evaluated	If Abnormal, specify findings
Head	☐	☐	☐	
Ears	☐	☐	☐	
Eyes	☐	☐	☐	
Mouth	☐	☐	☐	
Skin Appearance	☐	☐	☐	
Cardiovascular	☐	☐	☐	
Pulmonary	☐	☐	☐	
Abdomen	☐	☐	☐	
Hips and Legs	☐	☐	☐	
Genitalia	☐	☐	☐	

Site		Visit Name	TD 21	Not Done	
Patient		Patient Initials		Visit Date	

CHEMISTRY

Sample Date: **dd-mmm-yyyy** **Time:** **hh:mm** **(24-hour clock)**

Lab Name:

			Reference Ranges			If Abnormal	
Assay	**Result**	**Unit**	**Low**	**High**	**Flag**	**CS**	**NCS**
Sodium (Na)						☐	☐
Potassium (K)						☐	☐
Chloride						☐	☐
Calcium						☐	☐
BUN						☐	☐
Glucose						☐	☐
Creatinine						☐	☐
Total Protein						☐	☐
Albumin						☐	☐
AST (SGOT)						☐	☐
ALT (SGPT)						☐	☐
Alkaline Phosphatase						☐	☐

***CS - clinically significant, NCS - not clinically significant**

If any of these results are clinically significant (CS) at Baseline, list condition on the medical history page. If any of these results are clinically significant (CS) for Visits TD 1, 15, 21 and Mon 2 & 6 of Life, list condition on the Adverse Events page.

HEMATOLOGY

Sample Date: dd-mmm-yyyy **Time:** hh:mm

Lab Name

			Reference Ranges			If Abnormal	
	Result	**Unit**	**Low**	**High**	**Flag**	**CS**	**NCS**
WBC						☐	☐
RBC						☐	☐
Hemoglobin						☐	☐
Hematocrit						☐	☐
Platelets						☐	☐
Neutrophils						☐	☐
Lymphocytes						☐	☐
Monocytes						☐	☐
Eosinophils						☐	☐
Basophils						☐	☐

CS - clinically significant, NCS - not clinically significant

*If any of these results are clinically significant (CS) at Baseline, list condition on the Medical History page. If any of these results are clinically significant (CS) for Visits TD 1, 15, 21 and Mon 2 & 6 of Life, , list condition on the Adverse Events page.

Site		Visit Name	TD 21	Not Done	
Subject		Patient Initials		Visit Date	

URINALYSIS

Sample Date: _____ (dd-mmm-yyyy) **Time:** _____ (hh:mm) **Lab ID:** _____

Urine Parameter	Result	If Abnormal CS	If Abnormal NCS
Specific Gravity		☐	☐
pH		☐	☐

Component	Result	If Abnormal CS	If Abnormal NCS
Protein		☐	☐
Glucose		☐	☐
Ketones		☐	☐
Nitrite		☐	☐
Bilirubin		☐	☐
Blood		☐	☐
Leucocytes		☐	☐
Urobilinogen		☐	☐

Microscopic *(refer to completion guidelines)*

Component	Result	If Abnormal CS	If Abnormal NCS
WBC		☐	☐
RBC		☐	☐
Epithelial Cells		☐	☐
Bacteria		☐	☐
Casts		☐	☐
Crystals		☐	☐
Mucus		☐	☐

If any of these results are clinically significant (CS) as Baseline, list condition on the medical history page. If any of these results are clinically significant (CS) for Visits TD 1, 15, 21 and Mon 2 & 6 of Lief, list condition on the Adverse Events page.

THERMOREGULATION VITAL SIGNS - Neonate

Select Time Point from Drop-Down List	**Date of Vitals** dd-mmm-yyyy	**Time of Vitals** hh:mm	**Humidity**	**Incubator Temperature** C F	**Subject Temperature** C F	**Heart Rate** (beats/min)	**Respiration Rate** (breaths/min)
			%	☐ ☐	☐ ☐		
			%	☐ ☐	☐ ☐		
			%	☐ ☐	☐ ☐		
			%	☐ ☐	☐ ☐		
			%	☐ ☐	☐ ☐		
			%	☐ ☐	☐ ☐		
			%	☐ ☐	☐ ☐		
			%	☐ ☐	☐ ☐		
			%	☐ ☐	☐ ☐		
			%	☐ ☐	☐ ☐		

Report any clinical significant changes that are a clinical worsening of baseline on the Adverse Events page.

Site		Visit Name	MON 2 OF LIFE	Not Done	
Subject		Patient Initials		Visit Date	

PHYSICAL EXAM - FULL - Neonate

Date of Physical Exam: _____
dd-mmm-yyyy

Length: _____ ☐ CM ☐ IN **Weight:** _____ ☐ KG ☐ LB
Head Circumfrence: _____ ☐ CM ☐ IN

Vital Signs:
1. Temperature: _____ ☐ C ☐ F **2. Respiration Rate:** _____ Breaths per minute
3. Blood Pressure: _____ _____ mmHg **4. Heart Rate:** _____ Beats per minute
Systolic / Diastolic

Body System	Normal	Abnormal	Not Evaluated	If Abnormal, specify findings
Head	☐	☐	☐	
Ears	☐	☐	☐	
Eyes	☐	☐	☐	
Mouth	☐	☐	☐	
Skin Appearance	☐	☐	☐	
Cardiovascular	☐	☐	☐	
Pulmonary	☐	☐	☐	
Abdomen	☐	☐	☐	
Hips and Legs	☐	☐	☐	
Genitalia	☐	☐	☐	

CHEMISTRY

Sample Date: **dd-mmm-yyyy** **Time:** **hh:mm** **(24-hour clock)**

Lab Name:

Assay	Result	Unit	Reference Ranges Low	Reference Ranges High	Flag	If Abnormal CS	If Abnormal NCS
Sodium (Na)						☐	☐
Potassium (K)						☐	☐
Chloride						☐	☐
Calcium						☐	☐
BUN						☐	☐
Glucose						☐	☐
Creatinine						☐	☐
Total Protein						☐	☐
Albumin						☐	☐
AST (SGOT)						☐	☐
ALT (SGPT)						☐	☐
Alkaline Phosphatase						☐	☐

***CS - clinically significant, NCS - not clinically significant**

If any of these results are clinically significant (CS) at Baseline, list condition on the medical history page. If any of these results are clinically significant (CS) for Visits TD 1, 15, 21 and Mon 2 & 6 of Life, list condition on the Adverse Events page.

HEMATOLOGY

Sample Date: dd-mmm-yyyy **Time:** hh:mm

Lab Name

	Result	Unit	Reference Ranges Low	Reference Ranges High	Flag	If Abnormal CS	If Abnormal NCS
WBC						☐	☐
RBC						☐	☐
Hemoglobin						☐	☐
Hematocrit						☐	☐
Platelets						☐	☐
Neutrophils						☐	☐
Lymphocytes						☐	☐
Monocytes						☐	☐
Eosinophils						☐	☐
Basophils						☐	☐

CS - clinically significant, NCS - not clinically significant

*If any of these results are clinically significant (CS) at Baseline, list condition on the Medical History page. If any of these results are clinically significant (CS) for Visits TD 1, 15, 21 and Mon 2 & 6 of Life, , list condition on the Adverse Events page.

Site		Visit Name	MON 2 OF LIFE	Not Done	
Subject		Patient Initials		Visit Date	

URINALYSIS

Sample Date: _____ (dd-mmm-yyyy) **Time:** _____ (hh:mm) **Lab ID:** _____

Urine Parameter	Result	If Abnormal CS	If Abnormal NCS
Specific Gravity		☐	☐
pH		☐	☐

Component	Result	If Abnormal CS	If Abnormal NCS
Protein		☐	☐
Glucose		☐	☐
Ketones		☐	☐
Nitrite		☐	☐
Bilirubin		☐	☐
Blood		☐	☐
Leucocytes		☐	☐
Urobilinogen		☐	☐

Microscopic *(refer to completion guidelines)*

Component	Result	If Abnormal CS	If Abnormal NCS
WBC		☐	☐
RBC		☐	☐
Epithelial Cells		☐	☐
Bacteria		☐	☐
Casts		☐	☐
Crystals		☐	☐
Mucus		☐	☐

If any of these results are clinically significant (CS) as Baseline, list condition on the medical history page. If any of these results are clinically significant (CS) for Visits TD 1, 15, 21 and Mon 2 & 6 of Lief, list condition on the Adverse Events page.

Blood Sample Collection Date: dd-mmm-yyyy

Accession Number:

PK SAMPLING - Neonate

Date of PK Sampling	**Sampling Time**
dd-mmm-yyyy	24-hour clock

GROWTH AND DEVELOPMENT BAYLEY SCALES II & III AND DENVER- Neonate

Growth and Development Assessments

Date of Assessment: dd-mmm-yyyy

Date of Birth: dd-mmm-yyyy

Chronological Age:	months	days
Adjustment for Prematurity:	months	days
Corrected Age:	months	days

Bayley Scales of Infant Development II ☐ ND

Assessment Scale	**Raw Score**	**Mental Development Index**
Mental Scale		
Assessment Scale	**Raw Score**	**Psychomotor Development Index**
Motor Scale		

Bayley Scales of Infant Development III ☐ ND

Assessment Scale	**Sum of Scaled Scores**	**Composite Score**
Motor Composite Score		
Cognitive Comprehensive Score		

Denver Development Screnning Test II ☐ ND

Component	**Select Test Results from Drop Down List***
Personal-Social	
Fine Motor	
Gross Motor	

Other Growth and Development Assessment ☐ Yes ☐ No

If yes, please specify:

SWEAT RATE - Neonate Sibling

Date of Assessment

dd-mmm-yyyy

SWEAT RATE

Assay	Result	Unit	Start Time hh:mm	End Time hh:mm
Sweat Volume*		uL		

The macroduct sweat collector is held in place for approximately 30 minutes. See protocol for futher instructions.

SWEAT DUCT DENSITY

Date of Assessment:

dd-mmm-yyyy

Dry Eye Assessment:

Date of Assessment:
dd-mmm-yyyy

Exam	Select Result for Left Eye from Drop Down List	Select Result for Right Eye from Drop Down List
Corneal Exam		

Exam	Select Result for Left Eye from Drop Down List	Select Result for Right Eye from Drop Down List
Eyelid Exam for Melbomian Gland Openings		

Was Non-Invasive Break Up Time (NIBUT) assessed? ☐ Yes ☐ No ☐ Unable to assess

NIBUT Results

Right Eye ____ sec Left Eye ____ sec

Other findings, please comment:

Site		Visit Name	MON 4 OF LIFE	Not Done	
Subject		Patient Initials		Visit Date	

PHYSICAL EXAM - FULL - Neonate

Date of Physical Exam: _____
dd-mmm-yyyy

Length: _____ ☐ CM ☐ IN **Weight:** _____ ☐ KG ☐ LB
Head Circumfrence: _____ ☐ CM ☐ IN

Vital Signs:
1. Temperature: _____ ☐ C ☐ F **2. Respiration Rate:** _____ Breaths per minute
3. Blood Pressure: _____ _____ mmHg **4. Heart Rate:** _____ Beats per minute
Systolic / Diastolic

Body System	Normal	Abnormal	Not Evaluated	If Abnormal, specify findings
Head	☐	☐	☐	
Ears	☐	☐	☐	
Eyes	☐	☐	☐	
Mouth	☐	☐	☐	
Skin Appearance	☐	☐	☐	
Cardiovascular	☐	☐	☐	
Pulmonary	☐	☐	☐	
Abdomen	☐	☐	☐	
Hips and Legs	☐	☐	☐	
Genitalia	☐	☐	☐	

GROWTH AND DEVELOPMENT BAYLEY SCALES II & III AND DENVER- Neonate

Growth and Development Assessments

Date of Assessment: dd-mmm-yyyyy

Date of Birth: dd-mmm-yyyyy

Chronological Age:		months		days
Adjustment for Prematurity:		months		days
Corrected Age:		months		days

Bayley Scales of Infant Development II ☐ ND

Assessment Scale	**Raw Score**	**Mental Development Index**
Mental Scale		
Assessment Scale	**Raw Score**	**Psychomotor Development Index**
Motor Scale		

Bayley Scales of Infant Development III ☐ ND

Assessment Scale	**Sum of Scaled Scores**	**Composite Score**
Motor Composite Score		
Cognitive Comprehensive Score		

Denver Development Screnning Test II ☐ ND

Component	**Select Test Results from Drop Down List***
Personal-Social	
Fine Motor	
Gross Motor	

Other Growth and Development Assessment ☐ Yes ☐ No

If yes, please specify:

Site		Visit Name	MON 6 OF LIFE	Not Done	
Subject		Patient Initials		Visit Date	

PHYSICAL EXAM - FULL - Neonate

Date of Physical Exam: _____
dd-mmm-yyyy

Length: _____ ☐ CM ☐ IN **Weight:** _____ ☐ KG ☐ LB
Head Circumfrence: _____ ☐ CM ☐ IN

Vital Signs:
1. Temperature: _____ ☐ C ☐ F **2. Respiration Rate:** _____ Breaths per minute
3. Blood Pressure: _____ _____ mmHg **4. Heart Rate:** _____ Beats per minute
Systolic / Diastolic

Body System	Normal	Abnormal	Not Evaluated	If Abnormal, specify findings
Head	☐	☐	☐	
Ears	☐	☐	☐	
Eyes	☐	☐	☐	
Mouth	☐	☐	☐	
Skin Appearance	☐	☐	☐	
Cardiovascular	☐	☐	☐	
Pulmonary	☐	☐	☐	
Abdomen	☐	☐	☐	
Hips and Legs	☐	☐	☐	
Genitalia	☐	☐	☐	

Site		Visit Name	MON 6 OF LIFE	Not Done	
Patient		Patient Initials		Visit Date	

CHEMISTRY

Sample Date: **dd-mmm-yyyy** **Time:** **hh:mm** **(24-hour clock)**

Lab Name:

			Reference Ranges			If Abnormal	
Assay	**Result**	**Unit**	**Low**	**High**	**Flag**	**CS**	**NCS**
Sodium (Na)						☐	☐
Potassium (K)						☐	☐
Chloride						☐	☐
Calcium						☐	☐
BUN						☐	☐
Glucose						☐	☐
Creatinine						☐	☐
Total Protein						☐	☐
Albumin						☐	☐
AST (SGOT)						☐	☐
ALT (SGPT)						☐	☐
Alkaline Phosphatase						☐	☐

***CS - clinically significant, NCS - not clinically significant**

If any of these results are clinically significant (CS) at Baseline, list condition on the medical history page. If any of these results are clinically significant (CS) for Visits TD 1, 15, 21 and Mon 2 & 6 of Life, list condition on the Adverse Events page.

HEMATOLOGY

Sample Date: dd-mmm-yyyy **Time:** hh:mm

Lab Name

			Reference Ranges			If Abnormal	
	Result	**Unit**	**Low**	**High**	**Flag**	**CS**	**NCS**
WBC						☐	☐
RBC						☐	☐
Hemoglobin						☐	☐
Hematocrit						☐	☐
Platelets						☐	☐
Neutrophils						☐	☐
Lymphocytes						☐	☐
Monocytes						☐	☐
Eosinophils						☐	☐
Basophils						☐	☐

CS - clinically significant, NCS - not clinically significant

*If any of these results are clinically significant (CS) at Baseline, list condition on the Medical History page. If any of these results are clinically significant (CS) for Visits TD 1, 15, 21 and Mon 2 & 6 of Life, , list condition on the Adverse Events page.

Site		Visit Name	MON 6 OF LIFE	Not Done	
Subject		Patient Initials		Visit Date	

URINALYSIS

Sample Date: _____ (dd-mmm-yyyy) **Time:** _____ (hh:mm) **Lab ID:** _____

Urine Parameter	Result	If Abnormal CS	If Abnormal NCS
Specific Gravity		☐	☐
pH		☐	☐

Component	Result	If Abnormal CS	If Abnormal NCS
Protein		☐	☐
Glucose		☐	☐
Ketones		☐	☐
Nitrite		☐	☐
Bilirubin		☐	☐
Blood		☐	☐
Leucocytes		☐	☐
Urobilinogen		☐	☐

Microscopic *(refer to completion guidelines)*

Component	Result	If Abnormal CS	If Abnormal NCS
WBC		☐	☐
RBC		☐	☐
Epithelial Cells		☐	☐
Bacteria		☐	☐
Casts		☐	☐
Crystals		☐	☐
Mucus		☐	☐

If any of these results are clinically significant (CS) as Baseline, list condition on the medical history page. If any of these results are clinically significant (CS) for Visits TD 1, 15, 21 and Mon 2 & 6 of Lief, list condition on the Adverse Events page.

Blood Sample Collection Date: dd-mmm-yyyy

Accession Number:

PK SAMPLING - Neonate

Date of PK Sampling	**Sampling Time**
dd-mmm-yyyy	24-hour clock

GROWTH AND DEVELOPMENT BAYLEY SCALES II & III AND DENVER- Neonate

Growth and Development Assessments

Date of Assessment: dd-mmm-yyyy

Date of Birth: dd-mmm-yyyy

Chronological Age:		months		days
Adjustment for Prematurity:		months		days
Corrected Age:		months		days

Bayley Scales of Infant Development II ☐ ND

Assessment Scale	**Raw Score**	**Mental Development Index**
Mental Scale		
Assessment Scale	**Raw Score**	**Psychomotor Development Index**
Motor Scale		

Bayley Scales of Infant Development III ☐ ND

Assessment Scale	**Sum of Scaled Scores**	**Composite Score**
Motor Composite Score		
Cognitive Comprehensive Score		

Denver Development Screnning Test II ☐ ND

Component	**Select Test Results from Drop Down List***
Personal-Social	
Fine Motor	
Gross Motor	

Other Growth and Development Assessment ☐ Yes ☐ No

If yes, please specify:

FACIAL DEVELOPMENT

Date of Facial Photographs

dd-mmm-yyyy

Photograph View

- ☐ Frontal
- ☐ Lateral
- ☐ Both Frontal and Lateral

If Lateral, select side

- ☐ Right
- ☐ Left
- ☐ Both Right and Left

Site		Visit Name	MON 6 OF LIFE	Not Done	
Subject		Patient Initials		Visit Date	

SWEAT RATE - Neonate Sibling

Date of Assessment

dd-mmm-yyyy

SWEAT RATE

Assay	Result	Unit	Start Time hh:mm	End Time hh:mm
Sweat Volume*		uL		

The macroduct sweat collector is held in place for approximately 30 minutes. See protocol for futher instructions.

SWEAT DUCT DENSITY

Date of Assessment:

dd-mmm-yyyy

Dry Eye Assessment:

Date of Assessment:
dd-mmm-yyyy

Exam	Select Result for Left Eye from Drop Down List	Select Result for Right Eye from Drop Down List
Corneal Exam		

	Select Result for Left Eye from Drop Down List	Select Result for Right Eye from Drop Down List
Eyelid Exam for Melbomian Gland Openings		

Was Non-Invasive Break Up Time (NIBUT) assessed? ☐ Yes ☐ No ☐ Unable to assess

NIBUT Results

Right Eye ____ sec Left Eye ____ sec

Other findings, please comment:

Site		Visit Name	UNSCHEDULED	Not Done	
Subject		Patient Initials		Visit Date	

PHYSICAL EXAM - FULL - Neonate

Date of Physical Exam: _____
dd-mmm-yyyy

Length: _____ ☐ CM ☐ IN **Weight:** _____ ☐ KG ☐ LB
Head Circumfrence: _____ ☐ CM ☐ IN

Vital Signs:
1. Temperature: _____ ☐ C ☐ F **2. Respiration Rate:** _____ Breaths per minute
3. Blood Pressure: _____ _____ mmHg **4. Heart Rate:** _____ Beats per minute
Systolic / Diastolic

Body System	Normal	Abnormal	Not Evaluated	If Abnormal, specify findings
Head	☐	☐	☐	
Ears	☐	☐	☐	
Eyes	☐	☐	☐	
Mouth	☐	☐	☐	
Skin Appearance	☐	☐	☐	
Cardiovascular	☐	☐	☐	
Pulmonary	☐	☐	☐	
Abdomen	☐	☐	☐	
Hips and Legs	☐	☐	☐	
Genitalia	☐	☐	☐	

Site		Visit Name	UNSCHEDULED	Not Done	
Patient		Patient Initials		Visit Date	

CHEMISTRY

Sample Date: _____ **Time:** _____ **(24-hour clock)**
dd-mmm-yyyy **hh:mm**

Lab Name: _____

			Reference Ranges			If Abnormal	
Assay	**Result**	**Unit**	**Low**	**High**	**Flag**	**CS**	**NCS**
Sodium (Na)						☐	☐
Potassium (K)						☐	☐
Chloride						☐	☐
Calcium						☐	☐
BUN						☐	☐
Glucose						☐	☐
Creatinine						☐	☐
Total Protein						☐	☐
Albumin						☐	☐
AST (SGOT)						☐	☐
ALT (SGPT)						☐	☐
Alkaline Phosphatase						☐	☐

***CS - clinically significant, NCS - not clinically significant**

If any of these results are clinically significant (CS) at Baseline, list condition on the medical history page. If any of these results are clinically significant (CS) for Visits TD 1, 15, 21 and Mon 2 & 6 of Life, list condition on the Adverse Events page.

HEMATOLOGY

Sample Date: dd-mmm-yyyy **Time:** hh:mm

Lab Name

			Reference Ranges			If Abnormal	
	Result	**Unit**	**Low**	**High**	**Flag**	**CS**	**NCS**
WBC						☐	☐
RBC						☐	☐
Hemoglobin						☐	☐
Hematocrit						☐	☐
Platelets						☐	☐
Neutrophils						☐	☐
Lymphocytes						☐	☐
Monocytes						☐	☐
Eosinophils						☐	☐
Basophils						☐	☐

CS - clinically significant, NCS - not clinically significant

*If any of these results are clinically significant (CS) at Baseline, list condition on the Medical History page. If any of these results are clinically significant (CS) for Visits TD 1, 15, 21 and Mon 2 & 6 of Life, , list condition on the Adverse Events page.

Site		Visit Name	UNSCHEDULED	Not Done	
Subject		Patient Initials		Visit Date	

PK SAMPLING - Neonate

Date of PK Sampling	**Sampling Time**
dd-mmm-yyyy	24-hour clock

Site		Visit Name	UNSCHEDULED	Not Done	
Subject		Patient Initials		Visit Date	

Blood Sample Collection Date:
dd-mmm-yyyy

Accession Number:

STUDY DRUG ADMINISTRATION - EDI200 - Neonate

Indicate Cohort: ☐ Cohort 1 - 3mg/kg ☐ Cohort 2 - 10mg/kg ☐ Cohort 3 - 20mg/kg

Day	Dose #	Total Daily Dose (mg)	Date dd/mmm/yyyy	Start Time of Infusion hh:mm	Stop Time of Infusion hh:mm	Complete Dose given?	If partial dose, provide actual dose given (in mg)
TD 0	1					☐ Yes ☐ No	
TD 4	2					☐ Yes ☐ No	
TD 7	3					☐ Yes ☐ No	
TD 11	4					☐ Yes ☐ No	
TD 14	5					☐ Yes ☐ No	

Site		Visit Name	AE	Not Done	
Subject		Patient Initials			

ADVERSE EVENT

AE Number

Did this adverse event cause the subject to discontinue from the study? ☐ **No** ☐ **Yes**

Event:

(Record only one event per page)

Date of Onset

dd-mmm-yyyy

Is this a Serious Adverse Event? ☐ **No** ☐ **Yes**

If yes, follow SAE instructions per Study Manual and indicate SAE criteria

- ☐ Death
- ☐ Life-threatening
- ☐ Hospitalization or prolonged hospitalization
- ☐ Persistent or significant disability/incapacity
- ☐ Congenital anomaly/birth defect
- ☐ Important medical event

Relationship of Event to Study Medication

- ☐ Not Related
- ☐ Unlikely Related
- ☐ Possibly Related
- ☐ Probably Related
- ☐ Definitely Related

Action Taken with Study Medication

- ☐ None
- ☐ Study Medication Interrupted
- ☐ Study Medication Discontinued

Grade per CTCAE v4.0:

- ☐ 1 - Mild
- ☐ 2 - Moderate
- ☐ 3 - Severe
- ☐ 4 - Life Threatening
- ☐ 5 - Death (related to AE)

Grade per Investigator Assessment

- ☐ 1 - Mild
- ☐ 2 - Moderate
- ☐ 3 - Severe
- ☐ 4 - Life Threatening
- ☐ 5 - Death (related to AE)

Treatment for Event *(check all that apply)*

- ☐ None
- ☐ Medication Administered
- ☐ Non-drug Therapy Administered
- ☐ Other Medication(s) Dose Modified

Site		Visit Name	AE	Not Done	
Subject		Patient Initials			

Outcome of Event

- ☐ Resolved*
- ☐ Death*
- ☐ Resolved with sequelae*
- ☐ Unresolved
- ☐ Unknown

Date Resolved/Death: dd-mmm-yyyy

** If checked, provide Date Resolved/Death*

Site		Visit Name	CON MEDS	Not Done	
Patient		Patient Initials			

CONCOMITANT MEDICATIONS

Medication	P	Indication*	Dose	Unit	Route	Regimen	Start Date dd-mmm-yyyy	End Date dd-mmm-yyyy	Ongoing	AE# or N/A

Check "P" if medication is given for prophylaxis

SUBJECT DISPOSITION

Did the subject receive all Study Drug per the protocol? ☐ Yes ☐ No ☐ N/A

If not, indicate the reason why subject did not receive all Study Drug

☐ Adverse Event AE #
☐ Withdrew Consent
☐ Lost to Follow Up
☐ Death
☐ Request for Termination by Sponsor or Regulatory Authorities
☐ Administrative / Other Reason, Specify below:

Did the subject complete the study? ☐ Yes ☐ No

If no, indicate the reason the subject did not complete the study:

☐ Adverse Event AE #
☐ Withdrew Consent
☐ Lost to Follow Up
☐ Death
☐ Request for Termination by Sponsor or Regulatory Authorities
☐ Administrative / Other Reason, Specify below:

Did the subject experience any AEs during the study? ☐ Yes ☐ No

Did the subject receive any Concomitant Medications? ☐ Yes ☐ No

Date of last day of study participation

Appendix 16.2- Listings

Table of Contents

Listing 16.2.1 Subject Disposition

Cohort	Patient ID	Gender	All Study Drug Received?	Reason Not all Study Drug Received	Completed the Study?	Reason Study Not Completed	AEs During Study?	Concomitant Medications During Study?	Date (Day) of Last Study Participation
Cohort 1	3063-001	M	Yes		Yes		Yes	Yes	24MAR2014(187)
Cohort 1	1012-001	M	Yes		Yes		Yes	Yes	30MAY2014(179)
Cohort 1	1068-001	M	Yes		Yes		Yes	Yes	27AUG2014(175)
Cohort 2	3064-001	M	Yes		Yes		Yes	Yes	03NOV2014(178)
Cohort 2	3005-001	M	Yes		Yes		Yes	Yes	12JAN2015(161)
Cohort 2	3063-002	F	Yes		Yes		Yes	Yes	21APR2015(170)
Cohort 2	3063-003	M	Yes		Yes		Yes	Yes	19MAY2015(174)
Cohort 2	3063-004	M	Yes		Yes		Yes	Yes	29JUN2015(175)
Cohort 3	1068-002	M	Yes		Yes		Yes	Yes	13AUG2015(167)
Cohort 3	3064-002	M	Yes		Yes		Yes	Yes	28SEP2015(172)
Siblings	1068-201	M	N/A		Yes		No	Yes	23APR2014
	3063-201	M	N/A		Yes		No	Yes	21APR2015
	3063-202	M	N/A		Yes		Yes	Yes	19MAY2015
	3064-201	M	N/A		Yes		No	Yes	04NOV2014

Listing 16.2.2 Protocol Deviations

Cohort	Patient ID	Gender	Deviation Date (Day)	Deviation Type	Deviation
Cohort 1	3063-001	M	18SEP2014(365)	Investigational Product	PD #1, Day 1, Subject 3063-001: Birth weight used for drug dose calculation instead of Baseline weight per protocol for all drug applications
			18SEP2013(0)	Procedure	PD #3, 15 minutes post dose vital signs, Subject 3063-001, 15 minute post dose vital signs were not performed after doses 1 to 5 of IP
Cohort 1	1012-001	M	03DEC2013(1)	Laboratory	PD #1, Day 1, Subject 1012-001: microscopy on the urinalysis was partially performed due to inadequate quantity of specimen
			30MAY2015(544)	Laboratory	PD #5, Month 6, Subject 1012-001: WBC, RBC, epithealial cells, bacteria, casts, crystals and mucus was not performed on the urine microscopy
			22JAN2014(51)	Procedure	PD #3, Month 2, Subject 1012-001: Dry eye assessment - NIBUT was not performed
			30MAY2015(544)	Procedure	PD #4, Month 6, Subject 1012-001: Dry eye assessment - NIBUT was not performed30-May-14
			02DEC2013(0)	Vital Signs	PD #2, 15 minutes post dose vital signs, Subject 1012-001, 15 minute post dose vital signs were not performed after doses of IP
Cohort 1	1068-001	M	02MAR2014(-3)	Laboratory	PD #2, Baseline, Subject 1068-001: microscopy on the urinalysis was partially performed due to unknown reason
			06MAR2014(1)	Laboratory	PD #4, Day 1, Subject 1068-001: microscopy on the urinalysis was not performed due to unknown reason
			06MAR2014(1)	Laboratory	PD #9, Day 1, Subject 1068-001: basophils on the hematology differential was not reported by the laboratory
			21MAR2014(16)	Laboratory	PD #5, Day 16, Subject 1068-001: Basophil on CBC not reported/performed due to unknown reason
			21MAR2014(16)	Laboratory	PD #6, Day 16, Subject 1068-001: microscopy on the urinalysis was partially performed due to unknown reason
			26MAR2014(21)	Laboratory	PD #7, Day 21, Subject 1068-001: Basophil on CBC not reported/performed due to unknown reason

Listing 16.2.2 Protocol Deviations

Cohort	Patient ID	Gender	Deviation Date (Day)	Deviation Type	Deviation
Cohort 1	1068-001	M	26MAR2014(21)	Laboratory	PD #8, Day 21, Subject 1068-001: microscopy on the urinalysis was partially performed due to unknown reason
			05MAR2014(0)	Vital Signs	PD #14, 15 minutes post dose vital signs, Subject 1068-001, 15 minute post dose vital signs were not performed after doses of IP
			09MAR2014(4)	Vital Signs	PD #3, Day 4, Subject 1068-001: 12 hour post dose BP not performed due to unknown reason
Cohort 2	3064-001	M	09MAY2014(0)	Laboratory	PD #5, Baseline: Subject 3064-001: Biochemistry - Glucose not measured in error
			09MAY2014(0)	Laboratory	PD #6, Day 1: Subject 3064-001: Haematology - Basophils not measured in error.
			10MAY2014(1)	Laboratory	PD # 9, Day 1: Subject 3064-001: Biochemistry - Glucose & Potassium not measured.
			12MAY2014(3)	Laboratory	PD #19, Unscheduled: Subject 3064-001: Time of blood sampling not recorded on following dates:12 May 2014 (haem only)13 May 201416 May 201419 May 2014
			25MAY2014(16)	Laboratory	PD # 14, Day 16: Subject 3064-001: Biochemistry - Glucose not measured.
			25MAY2014(16)	Laboratory	PD #15, Day 16: Subject 3064-001: Urinalysis - Specific Gravity not measured.
			25MAY2014(16)	Laboratory	PD #16, Day 16: Subject 3064-001: Urine Microscopy not done.
			30MAY2014(21)	Laboratory	PD #17, Day 21: Subject 3064-001: Biochemistry - Glucose not measured.
			30JUN2014(52)	Laboratory	PD #18, Month 2: Subject 3064-001: Time of blood sampling not recorded.
			07MAY2014(-2)	Procedure	PD #2, Baseline: Subject 3064-001: Urinalysis Time of sampling not recorded. Blood & Specific Gravity not tested
			08MAY2014(-1)	Procedure	PD #1, Screen: Subject 3064-001:Birth Length not recorded in error
			08MAY2014(-1)	Procedure	PD #3, Baseline: Subject 3064-001: Thermoregulation - time vitals returned to normal not recorded in error

Listing 16.2.2 Protocol Deviations

Cohort	Patient ID	Gender	Deviation Date (Day)	Deviation Type	Deviation
Cohort 2	3064-001	M	08MAY2014(-1)	Procedure	PD #4, Baseline: Subject 3064-001: Sweat Collection Test: site used filter paper weight rather than the Macroduct Collection System
			10MAY2014(1)	Procedure	PD #7, Day 1: Subject 3064-001: Urinalysis (dipstix) - Bilirubin & urobilinogen not measured.
			20MAY2014(11)	Procedure	PD #10, Day 11: Subject 3064-001: Vital Signs Post Dose:Time Points 20 hours & 24 hours - Respiratory rate not measured as neonate possibly feeding.
			23MAY2014(14)	Procedure	PD #11, Day 14: Subject 3064-001: Vital Signs:Time Point Pre-doseTime Point 1 hour post doseTime Point 4 hours post doseBlood Pressure not measured
			23MAY2014(14)	Procedure	PD #12, Day 14: Subject 3064-001:Time Point 16 hours post dose Heart Rate not measured.
			24MAY2014(15)	Procedure	PD #13, Day 15: Subject 3064-001: Weight & Blood Pressure not recorded.
			30JUN2014(52)	Procedure	PD #20, Month 2: Subject 3064-001: Physical Exam - length not measured.
			30JUN2014(52)	Procedure	PD #21, Month 2: Subject 3064-001: Urinalysis - Ph not recorded.
Cohort 2	3005-001	M	30JUL2014(-5)	I/E Criteria	PD # 1, Enrollment: Patient 3005-001: patient enrolled at age of 27 days old
			20AUG2014(16)	Laboratory	PD # 3, Day 7: patient 3005-001: PK sampling not performed for the following time point: 168 hrs post dose
			25AUG2014(21)	Laboratory	PD # 4: Day 21: BUN not done
			04AUG2014(0)	Vital Signs	PD # 2, Day 4: patient 3005-001: vitals signs have not been measured for the following points: 20 hrs post dose
Cohort 2	3063-002	F	02NOV2013(-365)	Procedure	PD #4, 15 minutes post dose vital signs, Subject 3063-002, 15 minute post dose vital signs were not performed after doses 1 to 5 of IP

Listing 16.2.2 Protocol Deviations

Cohort	Patient ID	Gender	Deviation Date (Day)	Deviation Type	Deviation
Cohort 2	3063-002	F	11FEB2014(-264)	Procedure	PD #8, Informed Consent Issue, Parents of Subject 3063-002 were not provided with the updated parental affected neonate ICF v.5.0, dated 11 Feb 2015 in error.
			29OCT2014(-4)	Procedure	PD #2, Screening Study Assessment has been performed prior to signed ICF
			04DEC2014(32)	Procedure	PD #7, Informed Consent Issue, Parents of Subject 3063-002 were not provided with the updated parental affected neonate ICF v.4.0, dated 04 Dec 2014 in error.
Cohort 2	3063-003	M	26NOV2014(0)	Procedure	PD #5, 15 minutes post dose vital signs, Subject 3063-003, 15 minute post dose vital signs were not performed after doses 1 to 5 of IP
			04DEC2014(8)	Procedure	PD #9, Informed Consent Issue, Parents of Subject 3063-003 were not provided with the updated parental affected neonate ICF v.4.0, dated 04 Dec 2014 in error.
			11FEB2015(77)	Procedure	PD #10, Informed Consent Issue, Parents of Subject 3063-003 were not provided with the updated parental affected neonate ICF v.5.0, dated 11 Feb 2015 in error.
Cohort 2	3063-004	M	16JUL2014(-173)	Procedure	PD #12, Informed Consent Issue, Mother of Subject 3063-004 was provided with the maternal ICF v.2.0, dated 08 Jul 2013 instead of v.3.0, dated 16 Jul 2014 in error.
			04DEC2014(-32)	Procedure	PD #9, Informed Consent Issue, Parents of Subject 3063-004 were not provided with the updated parental affected neonate ICF v.4.0, dated 04 Dec 2014 in error.
			05JAN2015(0)	Procedure	PD #6, 15 minutes post dose vital signs, Subject 3063-004, 15 minute post dose vital signs were not performed after doses 1 to 5 of IP
			11FEB2015(37)	Procedure	PD #10, Informed Consent Issue, Parents of Subject 3063-004 were not provided with the updated parental affected neonate ICF v.5.0, dated 11 Feb 2015 in error.
			19MAY2015(134)	Procedure	PD #11, Informed Consent Issue, Parents of Subject 3063-004 were not provided with the updated parental affected neonate ICF v.5.1, dated 19 May 2015 in error.

Listing 16.2.2 Protocol Deviations

Cohort	Patient ID	Gender	Deviation Date (Day)	Deviation Type	Deviation
Cohort 3	1068-002	M	25FEB2015(-2)	Laboratory	PD #10, Screen, Subject 1068-002 basophils on the hematology differential was not reported by the laboratory
			25FEB2015(-2)	Laboratory	PD #11, Screen, Subject 1068-002 bacteria, casts, crystals and mucus was not reported on urine microscopy
			28FEB2015(1)	Laboratory	PD #12, Day 1, Subject 1068-002 basophils on the hematology differential was not reported by the laboratory
			28FEB2015(1)	Laboratory	PD #13, Day 1, Subject 1068-002 bacteria, casts, crystals and mucus was not reported on urine microscopy
			12AUG2015(166)	Laboratory	PD# 15, Month 6, Subject 1068-002 protein on urinalysis was not done
			12AUG2015(166)	Laboratory	PD #16, Month 6, Subject 1068-002 bacteria, casts, crystals and mucus was not reported on urine microscopy
Siblings	3063-201	M	04DEC2014	Procedure	PD #13, Informed Consent Issue, Parents of Subject 3063-201 were not provided with the updated parental minor sibling ICF v.4.0, dated 04 Dec 2014 in error.
	3063-202	M	04DEC2014	Procedure	PD #13, Informed Consent Issue, Parents of Subject 3063-201 were not provided with the updated parental minor sibling ICF v.4.0, dated 04 Dec 2014 in error.
			04DEC2014	Procedure	PD # 15, Informed Consent Issue, Parents of Subject 3063-202 were not provided with the updated parental minor sibling ICF v.4.0, dated 04 Dec 2014 in error.
	3064-201	M	09MAY2014	Informed Consent	PD #2 Screen: Subject 3064-201: Sweat Duct Density Test performed prior to gaining written Informed Consent from Parents
			24MAY2014	Informed Consent	PD # 1, Screen: Subject 3064-201: Parents were provided with the incorrect version of the PIS / ICD (v.1.0 dated 11 Nov 2013).
			01SEP2014	Procedure	PD #3, Enrolment: Subject 3064-201: Physical Exam - head circumference not measured.
			03NOV2014	Procedure	PD #4, Enrolment: Subject 3064-201: eNO Testing attempted by failed due to insufficient co-operation by subject.

Listing 16.2.2 Protocol Deviations

Cohort	Patient ID	Gender	Deviation Date (Day)	Deviation Type	Deviation
Siblings	3064-201	M	04NOV2014	Procedure	PD #5, Enrolment: Subject 3064-201: Dental exam perfomed 1 day after neonate completed study.

Listing 16.2.4.1 Demographic Characteristics and Eligibility Criteria

Cohort	Patient ID	Age at Enrollment (Days)	Age at First Dose (Days)	Race	Gender	Ethnicity	HED Genetic Test Result	Subject Eligible?	Criterion Not Met	Specify Deviation	Waived?
Cohort 1	3063-001	1	3	White	M	Not Hispanic or Latino	DUPLICATION OF EXON 4 (= EXON 3 IN COMMON NOMENCLATURE)	Yes			
Cohort 1	1012-001	7	13	White	M	Not Hispanic or Latino	POSITIVE. DNA SEQUENCING IDENTIFIED THE ASN185_PRO196DEL VARIANT IN EXON 4 OF THE EDA GENE, WHICH WAS PREVIOUSLY DETECTED IN THIS INDIVIDUAL'S MOTHER	Yes			
Cohort 1	1068-001	10	13	White	M	Not Hispanic or Latino	HEMIZYGOUS C.502+1G>A, INTRON 2, EDA, PATHOGENIC	Yes			
Cohort 2	3064-001	7	10	Asian, White	M	Not Hispanic or Latino	HEMIZYGOUS FOR EDAC.467G>A	Yes			
Cohort 2	3005-001	22	27	White	M	Not Hispanic or Latino	PRESENCE OF HEMIZYGOT MUTATION C.739C>T(P.GLN247*)	No	I-02	PATIENT OLDER THAN 14 DAYS	Yes
Cohort 2	3063-002	8	12	White	F	Not Hispanic or Latino	EDA C.467_468DEL, P.R156QFSX2, HETEROZYGOUS	Yes			
Cohort 2	3063-003	7	9	White	M	Not Hispanic or Latino	EDA C.925-3C>G, HEMIZYGOUS	Yes			
Cohort 2	3063-004	2	5	White	M	Not Hispanic or Latino	EDA C.463C>T, P.R155C, HEMIZYGOUS	Yes			

Listing 16.2.4.1 Demographic Characteristics and Eligibility Criteria

Cohort	Patient ID	Age at Enrollment (Days)	Age at First Dose (Days)	Race	Gender	Ethnicity	HED Genetic Test Result	Subject Eligible?	Criterion Not Met	Specify Deviation Waived?
Cohort 3	1068-002	10	12	White	M	Not Hispanic or Latino	HEMIZYGOUS C.467G>T (P.ARG156LEU), EXON 2, EDA, PATHOGENIC	Yes		
Cohort 3	3064-002	7	10	White	M	Not Hispanic or Latino	EDA C.1049 G>T	Yes		
Siblings	1068-201	1084		White	M	Not Hispanic or Latino		Yes		
	3063-201	1289		White	M	Not Hispanic or Latino		Yes		
	3063-202	546		White	M	Not Hispanic or Latino		Yes		
	3064-201	1338		Asian, White	M	Not Hispanic or Latino		Yes		

Listing 16.2.4.2 Medical History

Cohort	Patient ID	Gender	Description of Condition or Procedure	System Organ Class	Preferred Term	Currently Active?	Year of Onset
Cohort 1	3063-001	M	SUSPECTED HYPOHIDROTIC ECTODERMAL DYSPLASIA BASED ON ANTENATAL TOOTH BUD COUNTS	CONGENITAL, FAMILIAL AND GENETIC DISORDERS	CONGENITAL ECTODERMAL DYSPLASIA	Yes	2013
			HIGH HAEMATOCRIT	INVESTIGATIONS	HAEMATOCRIT INCREASED	Yes	2013
			LOW MONOCYTES	INVESTIGATIONS	MONOCYTE COUNT DECREASED	Yes	2013
			HIGH NEUTROPHILS	INVESTIGATIONS	NEUTROPHIL COUNT INCREASED	Yes	2013
			LOW PLATELETS	INVESTIGATIONS	PLATELET COUNT DECREASED	Yes	2013
			AMNIOCENTESIS	INVESTIGATIONS	AMNIOCENTESIS	No	2013
Cohort 1	1012-001	M	X-LINKED HYPOHIDROTIC ECTODERMAL DYSPLASIA	CONGENITAL, FAMILIAL AND GENETIC DISORDERS	CONGENITAL ECTODERMAL DYSPLASIA	Yes	2013
			RETRUDED CHIN	CONGENITAL, FAMILIAL AND GENETIC DISORDERS	MICROGENIA	Yes	2013
			HEMOGLOBIN IN URINALYSIS	INVESTIGATIONS	HAEMOGLOBIN URINE PRESENT	Yes	2013
			LOW MCV ON CBC	INVESTIGATIONS	MEAN CELL VOLUME ABNORMAL	Yes	2013
			INTERMITTENT MUCUS THREADS IN URINALYSIS	INVESTIGATIONS	URINE ANALYSIS ABNORMAL	Yes	2013
			HYPERCALCEMIA	METABOLISM AND NUTRITION DISORDERS	HYPERCALCAEMIA	Yes	2013
			THIN SCALP HAIR	SKIN AND SUBCUTANEOUS TISSUE DISORDERS	ALOPECIA	Yes	2013
			THIN EYEBROWS	SKIN AND SUBCUTANEOUS TISSUE DISORDERS	ALOPECIA	Yes	2013
			SCURF AROUND EYES AND EYEBROWS	SKIN AND SUBCUTANEOUS TISSUE DISORDERS	DANDRUFF	Yes	2013
			DRY SKIN	SKIN AND SUBCUTANEOUS TISSUE DISORDERS	DRY SKIN	Yes	2013
			CONGENITAL ANKYLOGLOSSIA	CONGENITAL, FAMILIAL AND GENETIC DISORDERS	ANKYLOGLOSSIA CONGENITAL	No	2013
			LINGUAL FRENULECTOMY	SURGICAL AND MEDICAL PROCEDURES	TONGUE TIE OPERATION	No	2013
Cohort 1	1068-001	M	X-LINKED HYPOHIDROTIC ECTODERMAL DYSPLASIA	CONGENITAL, FAMILIAL AND GENETIC DISORDERS	CONGENITAL ECTODERMAL DYSPLASIA	Yes	2014
			MICROGNATHIA	CONGENITAL, FAMILIAL AND GENETIC DISORDERS	MICROGNATHIA	Yes	2014
			LOW SODIUM ON CMP	INVESTIGATIONS	BLOOD SODIUM DECREASED	Yes	2014
			LOW UREA NITROGEN (BUN) ON CMP	INVESTIGATIONS	BLOOD UREA DECREASED	Yes	2014
			HIGH MONOCYTES ON CBC	INVESTIGATIONS	MONOCYTE COUNT INCREASED	Yes	2014

Listing 16.2.4.2 Medical History

Cohort	Patient ID	Gender	Description of Condition or Procedure	System Organ Class	Preferred Term	Currently Active?	Year of Onset
Cohort 1	1068-001	M	HIGH ABSOLUTE MONOCYTES ON CBC	INVESTIGATIONS	MONOCYTE COUNT INCREASED	Yes	2014
			LOW PLASMA PROTEIN ON CMP	INVESTIGATIONS	PROTEIN TOTAL DECREASED	Yes	2014
			HIGH RED CELL DISTRIBUTION WIDTH (RDW-CV) ON CBC	INVESTIGATIONS	RED CELL DISTRIBUTION WIDTH INCREASED	Yes	2014
			LOW SPECIFIC GRAVITY ON URINALYSIS	INVESTIGATIONS	SPECIFIC GRAVITY URINE DECREASED	Yes	2014
			HEMANGIOMAS ON BILATERAL EYELIDS	NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	EYELID HAEMANGIOMA	Yes	2014
			BLUISH PERIORBITAL DISCOLORATIONS	SKIN AND SUBCUTANEOUS TISSUE DISORDERS	SKIN DISCOLOURATION	Yes	2014
			LOW BLOOD GLUCOSE LEVEL	INVESTIGATIONS	BLOOD GLUCOSE DECREASED	No	2014
			CHEST X-RAY	INVESTIGATIONS	CHEST X-RAY	No	2014
			TRANSIENT NEONATE TACHYPNEA	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	NEONATAL TACHYPNOEA	No	2014
			INTERMITTENT SUBCOSTAL RETRACTIONS WITH BREATHING	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	USE OF ACCESSORY RESPIRATORY MUSCLES	No	2014
			CIRCUMCISION	SURGICAL AND MEDICAL PROCEDURES	CIRCUMCISION	No	2014
Cohort 2	3064-001	M	X-LINKED HYPOHIDROTIC ECTODERMAL DYSPLASIA	CONGENITAL, FAMILIAL AND GENETIC DISORDERS	CONGENITAL ECTODERMAL DYSPLASIA	Yes	2014
			HIGH BASOPHILS	INVESTIGATIONS	BASOPHIL COUNT INCREASED	Yes	2014
			LOW ALBUMIN	INVESTIGATIONS	BLOOD ALBUMIN DECREASED	Yes	2014
			HIGH MONOCYTES	INVESTIGATIONS	MONOCYTE COUNT INCREASED	Yes	2014
			HIGH PLATELET COUNT	INVESTIGATIONS	PLATELET COUNT INCREASED	Yes	2014
			HIGH WHITE CELL COUNT	INVESTIGATIONS	WHITE BLOOD CELL COUNT INCREASED	Yes	2014
			HYPERCALCAEMIA (CORRECTED CA+2)	METABOLISM AND NUTRITION DISORDERS	HYPERCALCAEMIA	Yes	2014
			DRY SKIN TO TORSO	SKIN AND SUBCUTANEOUS TISSUE DISORDERS	DRY SKIN	Yes	2014
			FLAKING SKIN TO TORSO	SKIN AND SUBCUTANEOUS TISSUE DISORDERS	SKIN EXFOLIATION	Yes	2014
			PERIORBITAL HYPERPIGMENTATION	SKIN AND SUBCUTANEOUS TISSUE DISORDERS	SKIN HYPERPIGMENTATION	Yes	2014
			WRINKLING TO SKIN PERIORBITALLY	SKIN AND SUBCUTANEOUS TISSUE DISORDERS	SKIN WRINKLING	Yes	2014
			JAUNDICE	HEPATOBILIARY DISORDERS	JAUNDICE	No	2014
			PHOTOTHERAPY	SURGICAL AND MEDICAL PROCEDURES	PHOTOTHERAPY	No	2014

Listing 16.2.4.2 Medical History

Cohort	Patient ID	Gender	Description of Condition or Procedure	System Organ Class	Preferred Term	Currently Active?	Year of Onset
Cohort 2	3005-001	M	ANEMIA	BLOOD AND LYMPHATIC SYSTEM DISORDERS	ANAEMIA	Yes	2014
			ELEVATED CHLORIDE	INVESTIGATIONS	BLOOD CHLORIDE INCREASED	Yes	2014
			ELEVATED EOSINOPHILS	INVESTIGATIONS	EOSINOPHIL COUNT INCREASED	Yes	2014
			LOW HEMATOCRIT	INVESTIGATIONS	HAEMATOCRIT DECREASED	Yes	2014
			LOW HEMOGLOBIN	INVESTIGATIONS	HAEMOGLOBIN DECREASED	Yes	2014
			ELEVATED LYMPHOCYTES	INVESTIGATIONS	LYMPHOCYTE COUNT INCREASED	Yes	2014
			ELEVATED MONOCYTES	INVESTIGATIONS	MONOCYTE COUNT INCREASED	Yes	2014
			ELEVATED NEUTROPHILS	INVESTIGATIONS	NEUTROPHIL COUNT INCREASED	Yes	2014
Cohort 2	3063-002	F	PRENATAL DIAGNOSIS OF A FETAL EDA MUTATION	CONGENITAL, FAMILIAL AND GENETIC DISORDERS	GENE MUTATION	Yes	2014
			SUSPECTED OLIGODONTIA BASED ON ANTENATAL TOOTH BUD COUNTS, CONFIRMED BY POSTNATAL X-RAY	CONGENITAL, FAMILIAL AND GENETIC DISORDERS	HYPODONTIA	Yes	2014
			HIGH CALCIUM	INVESTIGATIONS	BLOOD CALCIUM INCREASED	Yes	2014
			HIGH GLUCOSE	INVESTIGATIONS	BLOOD GLUCOSE INCREASED	Yes	2014
			LOW MONOCYTES	INVESTIGATIONS	MONOCYTE COUNT DECREASED	Yes	2014
			LOW RBC	INVESTIGATIONS	RED BLOOD CELL COUNT DECREASED	Yes	2014
			HYPOALBUMINEMIA	METABOLISM AND NUTRITION DISORDERS	HYPOALBUMINAEMIA	Yes	2014
			CHORIONIC VILLUS SAMPLING	INVESTIGATIONS	BIOPSY CHORIONIC VILLOUS	No	2014
Cohort 2	3063-003	M	ANEMIA	BLOOD AND LYMPHATIC SYSTEM DISORDERS	ANAEMIA	Yes	2014
			ANHIDROTIC ECTODERMAL DYSPLASIA	CONGENITAL, FAMILIAL AND GENETIC DISORDERS	CONGENITAL ECTODERMAL DYSPLASIA	Yes	2014
			ORAL CANDIDA INFECTION	INFECTIONS AND INFESTATIONS	ORAL CANDIDIASIS	Yes	2014
			HIGH CHLORIDE	INVESTIGATIONS	BLOOD CHLORIDE INCREASED	Yes	2014
			HIGH GLUCOSE	INVESTIGATIONS	BLOOD GLUCOSE INCREASED	Yes	2014
			LOW UREA	INVESTIGATIONS	BLOOD UREA DECREASED	Yes	2014
			HYPOALBUMINEMIA	METABOLISM AND NUTRITION DISORDERS	HYPOALBUMINAEMIA	Yes	2014
Cohort 2	3063-004	M	LEUKOPENIA	BLOOD AND LYMPHATIC SYSTEM DISORDERS	LEUKOPENIA	Yes	2015
			X-LINKED HYPOHIDROTIC ECTODERMAL DYPLASIA	CONGENITAL, FAMILIAL AND GENETIC DISORDERS	CONGENITAL ECTODERMAL DYSPLASIA	Yes	2015

Listing 16.2.4.2 Medical History

Cohort	Patient ID	Gender	Description of Condition or Procedure	System Organ Class	Preferred Term	Currently Active?	Year of Onset
Cohort 2	3063-004	M	PRENATAL SONOGRAPHIC DIAGNOSIS OF OLIGODONTIA	CONGENITAL, FAMILIAL AND GENETIC DISORDERS	HYPODONTIA	Yes	2014
			HYPERBILIRUBINEMIA	HEPATOBILIARY DISORDERS	HYPERBILIRUBINAEMIA	Yes	2015
			HIGH BASOPHILS	INVESTIGATIONS	BASOPHIL COUNT INCREASED	Yes	2015
			HIGH GLUCOSE	INVESTIGATIONS	BLOOD GLUCOSE INCREASED	Yes	2015
			LOW NEUTROPHILS	INVESTIGATIONS	NEUTROPHIL COUNT DECREASED	Yes	2015
			HYPERCHLOREMIA	METABOLISM AND NUTRITION DISORDERS	HYPERCHLORAEMIA	Yes	2015
Cohort 3	1068-002	M	TRACE ANISOCYTOSIS ON CBC	BLOOD AND LYMPHATIC SYSTEM DISORDERS	ANISOCYTOSIS	Yes	2015
			TRACE POIKILOCYTOSIS ON CBC	BLOOD AND LYMPHATIC SYSTEM DISORDERS	POIKILOCYTOSIS	Yes	2015
			1-10% TEAR DROP CELLS ON CBC	BLOOD AND LYMPHATIC SYSTEM DISORDERS	RED BLOOD CELL ABNORMALITY	Yes	2015
			XLHED	CONGENITAL, FAMILIAL AND GENETIC DISORDERS	CONGENITAL ECTODERMAL DYSPLASIA	Yes	2015
			PHIMOSIS	CONGENITAL, FAMILIAL AND GENETIC DISORDERS	PHIMOSIS	Yes	2015
			THRUSH	INFECTIONS AND INFESTATIONS	CANDIDA INFECTION	Yes	2015
			YEAST DIAPER RASH	INFECTIONS AND INFESTATIONS	CANDIDA NAPPY RASH	Yes	2015
			HIGH POTASSIUM ON CMP	INVESTIGATIONS	BLOOD POTASSIUM INCREASED	Yes	2015
			LOW UREA NITROGEN (BUN) ON CMP	INVESTIGATIONS	BLOOD UREA DECREASED	Yes	2015
			HIGH MONOCYTES ON CBC	INVESTIGATIONS	MONOCYTE COUNT INCREASED	Yes	2015
			HIGH PLATELETS ON CBC	INVESTIGATIONS	PLATELET COUNT INCREASED	Yes	2015
			INCREASED PLATELET ESTIMATE ON CBC	INVESTIGATIONS	PLATELET COUNT INCREASED	Yes	2015
			1-10% OVALOCYTES ON CBC	INVESTIGATIONS	RED BLOOD CELL ELLIPTOCYTES PRESENT	Yes	2015
			1-10% MICROCYTES ON CBC	INVESTIGATIONS	RED BLOOD CELL MACROCYTES PRESENT	Yes	2015
			1-10% MACROCYTES ON CBC	INVESTIGATIONS	RED BLOOD CELL MACROCYTES PRESENT	Yes	2015
			1-10% SCHISTOCYTES ON CBC	INVESTIGATIONS	RED BLOOD CELL SCHISTOCYTES PRESENT	Yes	2015
			HIGH RED CELL DISTRIBUTION WIDTH (RDW-CV) ON CBC	INVESTIGATIONS	RED CELL DISTRIBUTION WIDTH INCREASED	Yes	2015
			TONGUE TIE	CONGENITAL, FAMILIAL AND GENETIC DISORDERS	ANKYLOGLOSSIA CONGENITAL	No	2015
			JAUNDICE	HEPATOBILIARY DISORDERS	JAUNDICE	No	2015
			SMALL ABRASION ON LEFT SCALP FROM FALL	INJURY, POISONING AND PROCEDURAL COMPLICATIONS	SKIN ABRASION	No	2015
			SKULL X-RAY	INVESTIGATIONS	SKULL X-RAY	No	2015

Listing 16.2.4.2 Medical History

Cohort	Patient ID	Gender	Description of Condition or Procedure	System Organ Class	Preferred Term	Currently Active?	Year of Onset
Cohort 3	1068-002	M	FRENULUM OF TONGUE CLIPPED	SURGICAL AND MEDICAL PROCEDURES	TONGUE TIE OPERATION	No	2015
Cohort 3	3064-002	M	CRUMPLED AND OVERFOLDED EARS	CONGENITAL, FAMILIAL AND GENETIC DISORDERS	ANOMALY OF EXTERNAL EAR CONGENITAL	Yes	2015
			X-LINKED HYPOHIDROTIC ECTODERMAL DYSPLASIA	CONGENITAL, FAMILIAL AND GENETIC DISORDERS	CONGENITAL ECTODERMAL DYSPLASIA	Yes	2015
			SPARSE EYELASHES	EYE DISORDERS	GROWTH OF EYELASHES	Yes	2015
			UNDERDEVELOPED ALVEOLAR RIDGES (PATCHY)	GASTROINTESTINAL DISORDERS	DENTAL ALVEOLAR ANOMALY	Yes	2015
			HIGH ALKALINE PHOSPHATASE	INVESTIGATIONS	BLOOD ALKALINE PHOSPHATASE INCREASED	Yes	2015
			LOW CREATININE	INVESTIGATIONS	BLOOD CREATININE DECREASED	Yes	2015
			HIGH HAEMATOCRIT	INVESTIGATIONS	HAEMATOCRIT INCREASED	Yes	2015
			HIGH HAEMOGLOBIN	INVESTIGATIONS	HAEMOGLOBIN INCREASED	Yes	2015
			NASAL CONGESTION	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	NASAL CONGESTION	Yes	2015
			DRY SKIN	SKIN AND SUBCUTANEOUS TISSUE DISORDERS	DRY SKIN	Yes	2015
			SPARSE BROWS	SKIN AND SUBCUTANEOUS TISSUE DISORDERS	HAIR GROWTH ABNORMAL	Yes	2015
			PEELING SKIN	SKIN AND SUBCUTANEOUS TISSUE DISORDERS	SKIN EXFOLIATION	Yes	2015
Siblings	3063-201	M	ANODONTIA	CONGENITAL, FAMILIAL AND GENETIC DISORDERS	ANODONTIA	Yes	2012
			HYPOHIDROTIC ECTODERMAL DYSPLASIA	CONGENITAL, FAMILIAL AND GENETIC DISORDERS	CONGENITAL ECTODERMAL DYSPLASIA	Yes	2011
			PSYCHOMOTOR RETARDATION	PSYCHIATRIC DISORDERS	PSYCHOMOTOR RETARDATION	Yes	2014
			FREQUENT NOSEBLEEDS	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	EPISTAXIS	Yes	2012
			HYPERTHERMIE EPISODES	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	HYPERTHERMIA	No	2012
			VIRAL PNEUMONIA	INFECTIONS AND INFESTATIONS	PNEUMONIA VIRAL	No	2012
			REPEATED HOARSENESS	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	DYSPHONIA	No	2012

Listing 16.2.4.2 Medical History

Cohort	Patient ID	Gender	Description of Condition or Procedure	System Organ Class	Preferred Term	Currently Active?	Year of Onset
Siblings	3063-202	M	HYPOHIDROTIC ECTODERMAL DYSPLASIA	CONGENITAL, FAMILIAL AND GENETIC DISORDERS	CONGENITAL ECTODERMAL DYSPLASIA	Yes	2013
			OLIGODONTIA	CONGENITAL, FAMILIAL AND GENETIC DISORDERS	HYPODONTIA	Yes	2014
			REPEATED HOARSENESS	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	DYSPHONIA	Yes	2014
			ECZEMA	SKIN AND SUBCUTANEOUS TISSUE DISORDERS	ECZEMA	Yes	2014
			HYPERTHERMIC EPISODES	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	HYPERTHERMIA	No	2013
			ACUTE BRONCHITIS	INFECTIONS AND INFESTATIONS	BRONCHITIS	No	2014
	3064-201	M	X-LINKED ECTODERMAL DYSPLASIA	CONGENITAL, FAMILIAL AND GENETIC DISORDERS	CONGENITAL ECTODERMAL DYSPLASIA	Yes	2010
			ASTHMA	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	ASTHMA	Yes	2011
			ECZEMA	SKIN AND SUBCUTANEOUS TISSUE DISORDERS	ECZEMA	Yes	2011
			BRONCHIOLITIS -INFLUENZA (NPA POSITIVE)	INFECTIONS AND INFESTATIONS	BRONCHIOLITIS	No	2010
			BRONCHIOLITIS	INFECTIONS AND INFESTATIONS	BRONCHIOLITIS	No	2011
			BRONCHIOLITIS=SYNCITIAL VIRUS (NPA POSITIVE)	INFECTIONS AND INFESTATIONS	RESPIRATORY SYNCYTIAL VIRUS BRONCHIOLITIS	No	2011

Listing 16.2.4.3 Concomitant Medications

Cohort	Patient ID	Gender	Start Date(Day)	Stop Date(Day)	Medication	ATC1 Name	Preferred Term	Dose	Unit	Route	Indication	Regimen	TE?	AE #
Cohort 1	3063-001	M	UK/UNK/UNK	UK/UNK/UNK	OXYGEN	ALIMENTARY TRACT AND METABOLISM	OXYGEN	1.5	L	BY INHALATION	BRONCHITIS	UNK		12
			UK/UNK/UNK	UK/UNK/UNK	GLUCOSE-ELECTROLYTE SOLUTION	BLOOD AND BLOOD FORMING ORGANS	ELECTROLYTES NOS W/GLUCOSE	UNK	UNK	UNK	BRONCHITIS	UNK		12
			UK/UNK/UNK	UK/UNK/UNK	IPRATROPIUM BROMIDE	CARDIOVASCULAR SYSTEM	IPRATROPIUM BROMIDE	UNK	UNK	UNK	OBSTRUCTIVE BRONCHITIS	UNK		11
			UK/UNK/UNK	UK/UNK/UNK	METHYLPREDNISOLON CREAM	DERMATOLOGICALS	METHYLPREDNISOLONE	UNK	UNK	TOPICAL	ECZEMA	UNK		N/A
			UK/UNK/UNK	UK/UNK/UNK	PARACETAMOL	NERVOUS SYSTEM	PARACETAMOL	180	MG	ORALLY	BRONCHITIS/FEVER	ONCE		12
			UK/UNK/UNK	UK/UNK/UNK	CETIRIZIN	RESPIRATORY SYSTEM	CETIRIZINE HYDROCHLORIDE	2 X 2.5	MG	ORALLY	ALLERGY	UNK		N/A
			UK/UNK/UNK	UK/UNK/UNK	CORTISONE	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	CORTISONE	UNK	UNK	UNK	OBSTRUCTIVE BRONCHITIS	UNK		11
			16SEP2013(-2)	30SEP2013(12)	GLUCOSE	BLOOD AND BLOOD FORMING ORGANS	GLUCOSE	20	%	PO	SEDATION	PRN		N/A
			17SEP2013(-1)	17SEP2013(-1)	ESKETAMINE	NERVOUS SYSTEM	ESKETAMINE	3.0	MG	IV	SEDATION	BID		N/A
			17SEP2013(-1)	17SEP2013(-1)	MIDAZOLAM	NERVOUS SYSTEM	MIDAZOLAM	0.4	MG	IV	SEDATION	QD		N/A
			17SEP2013(-1)	17SEP2013(-1)	MIDAZOLAM	NERVOUS SYSTEM	MIDAZOLAM	0.3	MG	IV	SEDATION	QD		N/A
			17SEP2013(-1)	03OCT2013(15)	SODIUM CHLORIDE	ALIMENTARY TRACT AND METABOLISM	SODIUM CHLORIDE	0.9	%	IV	TO KEEP CENTRAL LINE OPEN	CONTINUOUS		N/A
			18SEP2013(0)	18SEP2013(0)	PHYTOMENADIONE	BLOOD AND BLOOD FORMING ORGANS	PHYTOMENADIONE	2.0	MG	PO	PREVENTION OF BLEEDING IN NEWBORNS	QD	Yes	N/A
			19SEP2013(1)	19SEP2013(1)	ESKETAMINE	NERVOUS SYSTEM	ESKETAMINE	3.0	MG	IV	SEDATION	QD	Yes	N/A
			19SEP2013(1)	19SEP2013(1)	MIDAZOLAM	NERVOUS SYSTEM	MIDAZOLAM	0.4	MG	IV	SEDATION	QD	Yes	N/A

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Listing 16.2.4.3 Concomitant Medications

Cohort	Patient ID	Gender	Start Date(Day)	Stop Date(Day)	Medication	ATC1 Name	Preferred Term	Dose	Unit	Route	Indication	Regimen	TE?	AE #
Cohort 1	3063-001	M	19SEP2013(1)	20SEP2013(2)	GLUCOSE	BLOOD AND BLOOD FORMING ORGANS	GLUCOSE	10	%	IV	BREAST FEEDING NOT WELL ESTABLISHED THAT DAY	CONTINUOUS	Yes	N/A
			25SEP2013(7)	Cont.	ZYMAFLUOR D	ALIMENTARY TRACT AND METABOLISM	FLUOR-VIGANTOLETTEN /01518601/	500	I.U.	PO	PREVENTION OF RICKETS AND CARIES	QD	Yes	N/A
			03OCT2013(15)	03OCT2013(15)	ESKETAMINE	NERVOUS SYSTEM	ESKETAMINE	2.0	MG	IV	SEDATION	BID	Yes	N/A
			03OCT2013(15)	03OCT2013(15)	MIDAZOLAM	NERVOUS SYSTEM	MIDAZOLAM	0.4	MG	IV	SEDATION	BID	Yes	N/A
			18OCT2013(30)	18OCT2013(30)	PHYTOMENADIONE	BLOOD AND BLOOD FORMING ORGANS	PHYTOMENADIONE	2.0	MG	PO	PREVENTION FOR BLEEDING IN NEWBORNS	QD	Yes	N/A
			09DEC2013(82)	09DEC2013(82)	HEXYON	ANTIINFECTIVES FOR SYSTEMIC USE	BACTERIAL AND VIRAL VACCINES, COMBINED	UNK	UNK	IM	VACCINATION	1 DOSE	Yes	N/A
			09DEC2013(82)	09DEC2013(82)	PREVENAR 13	ANTIINFECTIVES FOR SYSTEMIC USE	PNEUMOCOCCAL VACCINE	UNK	UNK	IM	VACCINATION	1 DOSE	Yes	N/A
			20JAN2014(124)	20JAN2014(124)	HEXYON	ANTIINFECTIVES FOR SYSTEMIC USE	BACTERIAL AND VIRAL VACCINES, COMBINED	UNK	UNK	IM	VACCINATION	1 DOSE	Yes	N/A
			20JAN2014(124)	20JAN2014(124)	PREVENAR 13	ANTIINFECTIVES FOR SYSTEMIC USE	PNEUMOCOCCAL VACCINE	UNK	UNK	IM	VACCINATION	1 DOSE	Yes	N/A
			11FEB2014(146)*	12FEB2014(147)	OXYGEN	ALIMENTARY TRACT AND METABOLISM	OXYGEN	2	L/MIN	INH	RSV-INFECTION	CONTINUOUSLY	Yes	05
			11FEB2014(146)*	13FEB2014(148)	EPINEPHRINE	ALIMENTARY TRACT AND METABOLISM	EPINEPHRINE	0.5	MG	INH	RSV-INFECTION	TID	Yes	05
			11FEB2014(146)*	13FEB2014(148)	SODIUM CHLORIDE	ALIMENTARY TRACT AND METABOLISM	SODIUM CHLORIDE	3	%	INH	RSV-INFECTION	BID	Yes	05

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Listing 16.2.4.3 Concomitant Medications

Cohort	Patient ID	Gender	Start Date(Day)	Stop Date(Day)	Medication	ATC1 Name	Preferred Term	Dose	Unit	Route	Indication	Regimen	TE?	AE #
Cohort 1	3063-001	M	11FEB2014(146)*	13FEB2014(148)	SALBUTAMOL	RESPIRATORY SYSTEM	SALBUTAMOL	0.5	MG	INH	RSV-INFECTION	TID	Yes	05
			11FEB2014(146)*	14FEB2014(149)	GLUCOSE	BLOOD AND BLOOD FORMING ORGANS	GLUCOSE	5	%	IV	RSV-INFECTION	CONTINUOUS INFUSION	Yes	05
			25FEB2014(160)	25FEB2014(160)	HEXYON	ANTIINFECTIVES FOR SYSTEMIC USE	BACTERIAL AND VIRAL VACCINES, COMBINED	UNK	UNK	IM	VACCINATION	1 DOSE	Yes	N/A
			25FEB2014(160)	25FEB2014(160)	PREVENAR 13	ANTIINFECTIVES FOR SYSTEMIC USE	PNEUMOCOCCAL VACCINE	UNK	UNK	IM	VACCINATION	1 DOSE	Yes	N/A
			09JUL2014(294)	11JUL2014(296)	AZITHROMYCIN	ANTIINFECTIVES FOR SYSTEMIC USE	AZITHROMYCIN	15	MG/G	1 GTT (EYE DROP	EYE INFECTION	BID	Yes	07
			09JUL2014(294)	15JUL2014(300)	AMOXICILLIN	ANTIINFECTIVES FOR SYSTEMIC USE	AMOXICILLIN	250	MG	ORAL	OTITIS MEDIA	BID	Yes	08
			02SEP2014(349)	02SEP2014(349)	PRIORIX	ANTIINFECTIVES FOR SYSTEMIC USE	MEASLES MUMPS & RUBELLA LIVE ATTENUATED (FREE	NA	NA	SC	VACCINATION	1X	Yes	N/A
			02SEP2014(349)	02SEP2014(349)	VARILRIX	ANTIINFECTIVES FOR SYSTEMIC USE	VARICELLA ZOSTER VACCINE	NA	NA	SC	VACCINATION	1X	Yes	N/A
			11JUN2015(631)	11JUN2015(631)	PREDNISOLONE	ALIMENTARY TRACT AND METABOLISM	PREDNISOLONE	100	MG	RECTAL	OBSTRUCTIVE BRONCHITIS	ONCE	Yes	11
			11JUN2015(631)	15JUN2015(635)	SALBUTAMOL	RESPIRATORY SYSTEM	SALBUTAMOL	1.5	MG	INHALATION	OBSTRUCTIVE BRONCHITIS	UP TO 6 X DAILY	Yes	11
			12JUN2015(632)	12JUN2015(632)	OXYGEN	ALIMENTARY TRACT AND METABOLISM	OXYGEN	UNK	UNK	UNK	OBSTRUCTIVE BRONCHITIS	UNK	Yes	11
			12JUN2015(632)	13JUN2015(633)	GLUCOSE-ELECTROLYTE SOLUTION	BLOOD AND BLOOD FORMING ORGANS	ELECTROLYTES NOS W/GLUCOSE	UNK	UNK	UNK	OBSTRUCTIVE BRONCHITIS	UNK	Yes	11

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Listing 16.2.4.3 Concomitant Medications

Cohort	Patient ID	Gender	Start Date(Day)	Stop Date(Day)	Medication	ATC1 Name	Preferred Term	Dose	Unit	Route	Indication	Regimen	TE?	AE #
Cohort 1	3063-001	M	17SEP2015(729)	UK/UNK/UNK	IPRATROPIUM BROMIDE	CARDIOVASCULAR SYSTEM	IPRATROPIUM BROMIDE	UNK	UNK	UNK	BRONCHITIS	UNK	Yes	12
			17SEP2015(729)	UK/UNK/UNK	SALBUTAMOL	RESPIRATORY SYSTEM	SALBUTAMOL	2.5	MG	INHALATION	BRONCHITIS	UP TO 5 X DAILY	Yes	12
			17SEP2015(729)	17SEP2015(729)	PREDNISOLONE	ALIMENTARY TRACT AND METABOLISM	PREDNISOLONE	25	MG	INTRAVENIOUSLY	BRONCHITIS	ONCE	Yes	12
			17SEP2015(729)	17SEP2015(729)	PREDNISOLONE	ALIMENTARY TRACT AND METABOLISM	PREDNISOLONE	100	MG	RECTAL	BRONCHITIS	ONCE	Yes	12
Cohort 1	1012-001	M	27NOV2013(-5)	27NOV2013(-5)	LIDOCAINE-EPINEPHRINE 1%	NERVOUS SYSTEM	OCTOCAINE WITH EPINEPHRINE	1	ML	SC	PAIN CONTROL FOR BIOPSY	ONCE		N/A
			02DEC2013(0)	02DEC2013(0)	LIDOCAINE	CARDIOVASCULAR SYSTEM	LIDOCAINE	0.3	ML	SC	PAIN CONTROL FOR PICC	ONCE	Yes	N/A
			02DEC2013(0)	02DEC2013(0)	MORPHINE	NERVOUS SYSTEM	MORPHINE	0.2	MG	IV	PAIN CONTROL FOR PICC	ONCE	Yes	N/A
			02DEC2013(0)	02DEC2013(0)	SUCROSE 24%	VARIOUS	SUCROSE	1	ML	PO	PAIN CONTROL FOR PICC	ONCE	Yes	N/A
			02DEC2013(0)	18DEC2013(16)	0.9% NACL FLUSH	ALIMENTARY TRACT AND METABOLISM	SODIUM CHLORIDE	3	ML	IV	PERIPHERAL IV FLUSH	PRN	Yes	N/A
			02DEC2013(0)	18DEC2013(16)	HEPARIN FLUSH	BLOOD AND BLOOD FORMING ORGANS	HEPARIN	20	UNITS	IV	PICC FLUSH LOCK	QD	Yes	N/A
			03DEC2013(1)	03DEC2013(1)	LIDOCAINE-EPINEPHRINE 1%	NERVOUS SYSTEM	OCTOCAINE WITH EPINEPHRINE	1	ML	SC	PAIN CONTROL FOR BIOPSY	ONCE	Yes	N/A
			04DEC2013(2)	18DEC2013(16)	CHOLECALCIFEROL SOLUTION	ALIMENTARY TRACT AND METABOLISM	COLECALCIFEROL	400	UNITS	PO	DIETARY SUPPLEMENT	Q1D	Yes	N/A
			17DEC2013(15)	17DEC2013(15)	BUPIVACAINE 0.25%	NERVOUS SYSTEM	BUPIVACAINE	1	ML	SC	PAIN CONTROL FOR BIOPSY	ONCE	Yes	N/A
			17DEC2013(15)	17DEC2013(15)	LIDOCAINE-EPINEPHRINE 1%	NERVOUS SYSTEM	OCTOCAINE WITH EPINEPHRINE	1	ML	SC	PAIN CONTROL FOR BIOPSY	ONCE	Yes	N/A

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Listing 16.2.4.3 Concomitant Medications

Cohort	Patient ID	Gender	Start Date(Day)	Stop Date(Day)	Medication	ATC1 Name	Preferred Term	Dose	Unit	Route	Indication	Regimen	TE?	AE #
Cohort 1	1012-001	M	23DEC2013(21)	23DEC2013(21)	LIDOCAINE 4% CREAM	CARDIOVASCULAR SYSTEM	LIDOCAINE	0.3	ML	TOPICAL	PAIN CONTROL FOR CIRCUMCISION	ONCE	Yes	N/A
			19JAN2014(48)	19JAN2014(48)	ACETAMINOPHEN ORAL SUSPENSION	NERVOUS SYSTEM	PARACETAMOL	80	MG	PO	PAIN RELIEF FOR ROUTINE VACCINATIONS	ONCE	Yes	N/A
Cohort 1	1068-001	M	20FEB2014(-13)	20FEB2014(-13)	HEPATITIS B VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	HEPATITIS B VACCINE	0.5	ML	SQ	ROUTINE VACCINATION	ONCE		N/A
			02MAR2014(-3)	02MAR2014(-3)	MORPHINE	NERVOUS SYSTEM	MORPHINE	0.38	MG	PO	PAIN, PICC LINE PLACEMENT	ONCE		N/A
			02MAR2014(-3)	03MAR2014(-2)	SODIUM CHLORIDE (0.45% SOLN)	ALIMENTARY TRACT AND METABOLISM	SODIUM CHLORIDE	2	ML/HR	IV	PICC LINE MAINTENANCE	CONTINUOUS		N/A
			02MAR2014(-3)	06MAR2014(1)	HEPARIN LOCK FLUSH	BLOOD AND BLOOD FORMING ORGANS	HEPARIN SODIUM	5	UNITS	IV	PICC LINE MAINTENANCE	BID		N/A
			03MAR2014(-2)	03MAR2014(-2)	LIDOCAINE	CARDIOVASCULAR SYSTEM	LIDOCAINE	1.5	CC	SQ	PAIN, SKIN BIOPSY	ONCE		N/A
			05MAR2014(0)	25JUL2014(142)	CHOLECALCIFEROL	ALIMENTARY TRACT AND METABOLISM	COLECALCIFEROL	200	IU	PO	PREVENT VIT D DEFICIENCY	QD	Yes	N/A
			06MAR2014(1)	Cont.	AQUAPHOR	DERMATOLOGICALS	AQUAPHOR /01181901/	N/A	N/A	TOPICAL	DRY SKIN	PRN	Yes	N/A
			06MAR2014(1)	Cont.	AQUAPHOR	DERMATOLOGICALS	AQUAPHOR /01181901/	1	APPLICATION	TOPICAL	DRY SKIN	PRN	Yes	N/A
			06MAR2014(1)	06MAR2014(1)	LIDOCAINE	CARDIOVASCULAR SYSTEM	LIDOCAINE	1	CC	SQ	PAIN, SKIN BIOPSY	ONCE	Yes	N/A
			07MAR2014(2)	07MAR2014(2)	MORPHINE	NERVOUS SYSTEM	MORPHINE	0.36	MG	PO	PAIN, PICC LINE PLACEMENT	ONCE	Yes	N/A
			07MAR2014(2)	09MAR2014(4)	HEPARIN LOCK FLUSH	BLOOD AND BLOOD FORMING ORGANS	HEPARIN SODIUM	5	UNITS	IV	PICC LINE MAINTENANCE	BID	Yes	N/A

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Cohort	Patient ID	Gender	Start Date(Day)	Stop Date(Day)	Medication	ATC1 Name	Preferred Term	Dose	Unit	Route	Indication	Regimen	TE?	AE #
Cohort 1	1068-001	M	20MAR2014(15)	20MAR2014(15)	LIDOCAINE	CARDIOVASCULAR SYSTEM	LIDOCAINE	1	CC	SQ	PAIN, SKIN BIOPSY	ONCE	Yes	N/A
			25APR2014(51)	25APR2014(51)	H. INFLUENZAE TYPE B VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	HEMOPHILUS INFLUENZAE B VACCINES	0.5	ML	SQ	ROUTINE VACCINATION	ONCE	Yes	N/A
			25APR2014(51)	25APR2014(51)	HEPATITIS B VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	HEPATITIS B VACCINE	0.5	ML	SQ	ROUTINE VACCINATION	ONCE	Yes	N/A
			25APR2014(51)	25APR2014(51)	PNEUMOCOCCAL CONJUGATE VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	PNEUMOCOCCAL VACCINE	0.5	ML	SQ	ROUTINE VACCINATION	ONCE	Yes	N/A
			25APR2014(51)	25APR2014(51)	POLIO VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	POLIO VACCINE	0.5	ML	SQ	ROUTINE VACCINATION	ONCE	Yes	N/A
			25APR2014(51)	25APR2014(51)	ROTAVIRUS VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	ROTAVIRUS VACCINE	2	ML	PO	ROUTINE VACCINATION	ONCE	Yes	N/A
			25APR2014(51)	25APR2014(51)	DIPHTHERIA, TETANUS, AND PERTUSSIS VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	VACCIN IPAD D.T.C.	0.5	ML	SQ	ROUTINE VACCINATION	ONCE	Yes	N/A
			25APR2014(51)	26APR2014(52)	INFANT TYLENOL	NERVOUS SYSTEM	PARACETAMOL	0.5	ML	PO	PREVENTION OF DISCOMFORT POST VACCINE ADMINISTRATION	Q 6-8 HOURS PRN	Yes	N/A
			15JUL2014(132)	15JUL2014(132)	H. INFLUENZAE TYPE B VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	HEMOPHILUS INFLUENZAE B VACCINES	0.5	ML	SQ	ROUTINE VACCINATION	ONCE	Yes	N/A
			15JUL2014(132)	15JUL2014(132)	PNEUMOCOCCAL CONJUGATE VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	PNEUMOCOCCAL VACCINE	0.5	ML	SQ	ROUTINE VACCINATION	ONCE	Yes	N/A
			15JUL2014(132)	15JUL2014(132)	POLIO VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	POLIO VACCINE	0.5	ML	SQ	ROUTINE VACCINATION	ONCE	Yes	N/A

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Cohort	Patient ID	Gender	Start Date(Day)	Stop Date(Day)	Medication	ATC1 Name	Preferred Term	Dose	Unit	Route	Indication	Regimen	TE?	AE #
Cohort 1	1068-001	M	15JUL2014(132)	15JUL2014(132)	ROTAVIRUS VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	ROTAVIRUS VACCINE	2	ML	PO	ROUTINE VACCINATION	ONCE	Yes	N/A
			15JUL2014(132)	15JUL2014(132)	DIPHTHERIA, TETANUS, AND PERTUSSIS VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	VACCIN IPAD D.T.C.	0.5	ML	SQ	ROUTINE VACCINATION	ONCE	Yes	N/A
			15JUL2014(132)	15JUL2014(132)	INFANT TYLENOL	NERVOUS SYSTEM	PARACETAMOL	2.5	ML	PO	PREVENTION OF DISCOMFORT POST VACCINE ADMINISTRATIO N	Q 6-8 HOURS PRN	Yes	N/A
			05MAR2015(365)	09MAR2015(369)	INFANT MOTRIN	GENITO URINARY SYSTEM AND SEX HORMONES	IBUPROFEN	1.25	ML	PO	INTERMITTENT FEVER	PRN	Yes	01
			17MAR2015(377)	17MAR2015(377)	HEPATITIS A VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	HEPATITIS A VACCINE	N/A	N/A	IM	ROUTINE VACCINATION	ONCE	Yes	N/A
			17MAR2015(377)	17MAR2015(377)	MEASLES, MUMPS, AND RUBELLA VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	MEASLES MUMPS & RUBELLA LIVE ATTENUATED (FREE	N/A	N/A	IM	ROUTINE VACCINATION	ONCE	Yes	N/A
			17MAR2015(377)	17MAR2015(377)	VARICELLA VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	VARICELLA ZOSTER VACCINE	N/A	N/A	IM	ROUTINE VACCINATION	ONCE	Yes	N/A
			17MAR2015(377)	21MAR2015(381)	NYSTATIN CREAM	ALIMENTARY TRACT AND METABOLISM	NYSTATIN	N/A	N/A	TOPICA L	YEAST INFECTION ON BUTTOCKS	TID	Yes	N/A
			04OCT2015(578)	05OCT2015(579)	INFANT IBUPROFEN	GENITO URINARY SYSTEM AND SEX HORMONES	IBUPROFEN	1.875	ML	PO	PAIN WITH EAR INFECTION	Q 6-8 HOUR PRN	Yes	03
			05OCT2015(579)	15OCT2015(589)	CEFDINIR	ANTIINFECTIVES FOR SYSTEMIC USE	CEFDINIR	5	ML	PO	EAR INFECTION	BID	Yes	03

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Cohort 2	3064-001	M	UK-DEC-2014	UNKNOWN	SEPTRIN			5	MLS	ORAL	OTITIS MEDIA	BD		N/A
			08MAY2014(-1)	08MAY2014(-1)	LIGNOCAINE 0.5%	CARDIOVASCULAR SYSTEM	LIDOCAINE	1.5	MLS	SC	PAIN PREVENTION BEFORE SKIN BIOPSY	STAT		N/A
			08MAY2014(-1)	08MAY2014(-1)	AMETOP 0.5%	CARDIOVASCULAR SYSTEM	TETRACAINE	1.5	MLS	SUB CUT	SKIN BIOPSY	STAT		N/A
			08MAY2014(-1)	08MAY2014(-1)	EMLA	NERVOUS SYSTEM	EMLA /00675501/	1	N/A	TOPICAL	PAIN RELIEF PRIOR TO CANNULATION	STAT		N/A
			10MAY2014(1)	10MAY2014(1)	LIGNOCAINE 0.5%	CARDIOVASCULAR SYSTEM	LIDOCAINE	1.5	ML	S.C.	PAIN PREVENTION BEFORE SKIN BIOPSY	STAT	Yes	N/A
			10MAY2014(1)	11MAY2014(2)	NORMAL SALINE	ALIMENTARY TRACT AND METABOLISM	SODIUM CHLORIDE	2	MLS	IV	TO FLUSH IV LINE	BD	Yes	N/A
			10MAY2014(1)	14MAY2014(5)	POLYMYXIN	ANTIINFECTIVES FOR SYSTEMIC USE	POLYMYXIN	N/A	N/A	TOPICAL	BIOPSY WOUND COVERING	0D	Yes	N/A
			10MAY2014(1)	24MAY2014(15)	SALINE DROPS	ALIMENTARY TRACT AND METABOLISM	SODIUM CHLORIDE	2	MLS	NASAL	NASAL CRUSTING	PRN	Yes	N/A
			24MAY2014(15)	24MAY2014(15)	LIGNOCAINE 0.5%	CARDIOVASCULAR SYSTEM	LIDOCAINE	1.5	MLS	SC	PREVENTION OF PAIN BEFORE SKIN BIOPSY	STAT	Yes	N/A
			24MAY2014(15)	24MAY2014(15)	AMETOP 0.5%	CARDIOVASCULAR SYSTEM	TETRACAINE	0.5	MLS	SUB CUT	SKIN BIOPSY	STAT	Yes	N/A
			03JUL2014(55)	03JUL2014(55)	DIPHTHERIA IMMUNISATION	ANTIINFECTIVES FOR SYSTEMIC USE	DIPHTHERIA VACCINE	0.5	MLS	IM	CHILDHOOD IMMUNISATIONS	STAT	Yes	N/A
			03JUL2014(55)	03JUL2014(55)	HIB IMMUNISATION	ANTIINFECTIVES FOR SYSTEMIC USE	HAEMOPHILUS INFLUENZA TYPE B VACCINE	0.5	MLS	IM	CHILDHOOD IMMUNISATIONS	STAT	Yes	N/A

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Cohort 2	3064-001	M	03JUL2014(55)	03JUL2014(55)	HEPATITIS B IMMUNISATION	ANTIINFECTIVES FOR SYSTEMIC USE	HEPATITIS B VACCINE	0.5	MLS	IM	CHILDHOOD IMMUNISATIONS	STAT	Yes	N/A
			03JUL2014(55)	03JUL2014(55)	PERTUSSIS IMMUNISATION	ANTIINFECTIVES FOR SYSTEMIC USE	PERTUSSIS VACCINE	0.5	MLS	IM	CHILDHOOD IMMUNISATIONS	STAT	Yes	N/A
			03JUL2014(55)	03JUL2014(55)	PCV IMMUNISATION	ANTIINFECTIVES FOR SYSTEMIC USE	PNEUMOCOCCAL VACCINE	0.5	MLS	IM	CHILDHOOD IMMUNISATIONS	STAT	Yes	N/A
			03JUL2014(55)	03JUL2014(55)	POLIO IMMUNISATION	ANTIINFECTIVES FOR SYSTEMIC USE	POLIO VACCINE	0.5	MLS	IM	CHILDHOOD IMMUNISATIONS	STAT	Yes	N/A
			03JUL2014(55)	03JUL2014(55)	TETANUS IMMUNISATION	ANTIINFECTIVES FOR SYSTEMIC USE	TETANUS VACCINE	0.5	MLS	IM	CHILDHOOD IMMUNISATIONS	STAT	Yes	N/A
			03JUL2014(55)	03JUL2014(55)	PARACETAMOL	NERVOUS SYSTEM	PARACETAMOL	60	MGS	ORAL	POST IMMUNISATION	STAT	Yes	16
			09SEP2014(123)	09SEP2014(123)	DIPTHERIA IMMUNISATION	ANTIINFECTIVES FOR SYSTEMIC USE	DIPHTHERIA VACCINE	0.5	MLS	IM	CHILDHOOD IMMUNISATION PROGRAMME	STAT	Yes	N/A
			09SEP2014(123)	09SEP2014(123)	HIB IMMUNISATION	ANTIINFECTIVES FOR SYSTEMIC USE	HAEMOPHILUS INFLUENZA TYPE B VACCINE	0.5	MLS	IM	CHILDHOOD IMMUNISATION PROGRAMME	STAT	Yes	N/A
			09SEP2014(123)	09SEP2014(123)	HEP B IMMUNISATION	ANTIINFECTIVES FOR SYSTEMIC USE	HEPATITIS B VACCINE	0.5	MLS	IM	CHILDHOOD IMMUNISATION PROGRAMME	STAT	Yes	N/A
			09SEP2014(123)	09SEP2014(123)	MENINGITIS C IMMUNISATION	ANTIINFECTIVES FOR SYSTEMIC USE	MENINGOCOCCAL VACCINE	0.5	MLS	IM	CHILDHOOD IMMUNISATION PROGRAMME	STAT	Yes	N/A
			09SEP2014(123)	09SEP2014(123)	PERTUSSIS IMMUNISATION	ANTIINFECTIVES FOR SYSTEMIC USE	PERTUSSIS VACCINE	0.5	MLS	IM	CHILDHOOD IMMUNISATION PROGRAMME	STAT	Yes	N/A
			09SEP2014(123)	09SEP2014(123)	POLIO IMMUNISATION	ANTIINFECTIVES FOR SYSTEMIC USE	POLIO VACCINE	0.5	MLS	IM	CHILDHOOD IMMUNISATION PROGRAMME	STAT	Yes	N/A

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Listing 16.2.4.3 Concomitant Medications

Cohort	Patient ID	Gender	Start Date(Day)	Stop Date(Day)	Medication	ATC1 Name	Preferred Term	Dose	Unit	Route	Indication	Regimen	TE?	AE #
Cohort 2	3064-001	M	09SEP2014(123)	09SEP2014(123)	TETANUS IMMUNISATION	ANTIINFECTIVES FOR SYSTEMIC USE	TETANUS VACCINE	0.5	MLS	IM	CHILDHOOD IMMUNISATION PROGRAMME	STAT	Yes	N/A
			25OCT2014(169)	28OCT2014(172)	PARACETAMOL	NERVOUS SYSTEM	PARACETAMOL	60	MGS	ORAL	OTITIS MEDIA	PRN	Yes	17
			25OCT2014(169)	01NOV2014(176)	AUGMENTIN			2.5	MLS	ORAL	OTITIS MEDIA	BD	Yes	N/A
			25OCT2014(169)	02NOV2014(177)	AUGMENTIN	ANTIINFECTIVES FOR SYSTEMIC USE	AMOXICILLIN W/CLAVULANATE POTASSIUM	2.5	MLS	ORAL	OTITIS MEDIA	TDS	Yes	17
			09NOV2014(184)	15NOV2014(190)	ERYTHROMYCIN			UNK	UNK	ORAL	OTITIS MEDIA	UNK	Yes	N/A
			15JAN2015(251)	22JAN2015(258)	SEPTRIN			5	MLS	ORAL	OTITIS MEDIA	BD	Yes	N/A
			05FEB2015(272)	11FEB2015(278)	ERYTHROMYCIN			UNK	UNK	UNK	OTITIS MEDIA	UNK	Yes	N/A
			15FEB2015(282)	21FEB2015(288)	SOFRADEX			2	DROPS	TO LEFT EAR	OTITIS MEDIA	TDS	Yes	N/A
			22FEB2015(289)	28FEB2015(295)	GENTISONE			2	DROPS	BOTH EARS	OTITIS MEDIA	TDS	Yes	N/A
			01APR2015(327)	08APR2015(334)	GENTISONE			2	DROPS	BOTH EARS	OTITIS MEDIA	TDS	Yes	N/A
			01APR2015(327)	15APR2015(341)	AUGMENTIN			2.5	MLS	ORAL	OTITIS MEDIA	BD	Yes	N/A
Cohort 2	3005-001	M	10JUL2014(-25)	Cont.	UVESTEROL	ALIMENTARY TRACT AND METABOLISM	UVESTEROL	1	ML	PO	VITAMIN CARENCY	QD		N/A
			06AUG2014(2)	Cont.	FOLDINE/FOLIC ACID	BLOOD AND BLOOD FORMING ORGANS	FOLIC ACID	2.5	MG	PO	ANEMIA	EVERY 2 DAYS	Yes	N/A
			06AUG2014(2)	Cont.	FERROSTRANE	BLOOD AND BLOOD FORMING ORGANS	SODIUM FEREDETATE	5	MG	PO	ANEMIA	QD	Yes	N/A
			21SEP2014(48)	27SEP2014(54)	OROKEN	ANTIINFECTIVES FOR SYSTEMIC USE	CEFIXIME	1	NA	PO	PYELONEPHRYTIS	QD	Yes	5
			09OCT2014(66)	16OCT2014(73)	JOSACINE	ANTIINFECTIVES FOR SYSTEMIC USE	JOSAMYCIN	50	MG	PO	PHARYNGITIS	QD	Yes	3

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Listing 16.2.4.3 Concomitant Medications

Cohort	Patient ID	Gender	Start Date(Day)	Stop Date(Day)	Medication	ATC1 Name	Preferred Term	Dose	Unit	Route	Indication	Regimen	TE?	AE #
Cohort 2	3005-001	M	12NOV2014(100)	19NOV2014(107)	JOSACINE	ANTIINFECTIVES FOR SYSTEMIC USE	JOSAMYCIN	50	MG	PO	RHINOPHARYNGITIS	QD	Yes	2
			02DEC2014(120)	04DEC2014(122)	CELESTENE	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	CELESTENE /02907501/	0.075	MG	PO	RHINOPHARYNGITIS	QD	Yes	4
			02DEC2014(120)	08DEC2014(126)	JOSACINE	ANTIINFECTIVES FOR SYSTEMIC USE	JOSAMYCIN	50	MG	PO	RHINOPHARYNGITIS	QD	Yes	4
Cohort 2	3063-002	F	31OCT2014(-2)	Cont.	ZYMAFLUOR D	ALIMENTARY TRACT AND METABOLISM	FLUOR-VIGANTOLETTEN /01518601/	500	I.U.	P.O.	PROPHYLAXIS	ONCE DAILY		N/A
			31OCT2014(-2)	Cont.	ZYMAFLUOR D	ALIMENTARY TRACT AND METABOLISM	FLUOR-VIGANTOLETTEN /01518601/	500	IU	P.O.	PREVENTION OF RICKETS AND CARIES	QD		N/A
			31OCT2014(-2)	31OCT2014(-2)	MIDAZOLAM	NERVOUS SYSTEM	MIDAZOLAM	0.3	MG	IV	SEDATION	1 X		N/A
			31OCT2014(-2)	09NOV2014(7)	SODIUM CHLORIDE	ALIMENTARY TRACT AND METABOLISM	SODIUM CHLORIDE	0.9	%	IV	TO KEEP CENTRAL LINE OPEN	CONTINUOUS INFUSION		N/A
			31OCT2014(-2)	09NOV2014(7)	GLUCOSE	BLOOD AND BLOOD FORMING ORGANS	GLUCOSE	20	%	P.O.	SEDATION	PRN		N/A
			12NOV2014(10)	14NOV2014(12)	GLUCOSE	BLOOD AND BLOOD FORMING ORGANS	GLUCOSE	10	%	IV	TO KEEP CENTRAL LINE OPEN	CONTINUOUS INFUSION	Yes	02
			12NOV2014(10)	18NOV2014(16)	PIPERACILLIN	ANTIINFECTIVES FOR SYSTEMIC USE	PIPERACILLIN	0.3	G	IV	FEBRILE UPPER RESPIRATORY INFECTION	BID	Yes	02

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Listing 16.2.4.3 Concomitant Medications

Cohort	Patient ID	Gender	Start Date(Day)	Stop Date(Day)	Medication	ATC1 Name	Preferred Term	Dose	Unit	Route	Indication	Regimen	TE?	AE #
Cohort 2	3063-002	F	12NOV2014(10)	18NOV2014(16)	TOBRAMYCIN	ANTIINFECTIVES FOR SYSTEMIC USE	TOBRAMYCIN	15	MG	IV	FEBRILE UPPER RESPIRATORY INFECTION	QD	Yes	02
			22DEC2014(50)	22DEC2014(50)	HEXYON	ANTIINFECTIVES FOR SYSTEMIC USE	BACTERIAL AND VIRAL VACCINES, COMBINED	UNK	UNK	IM	VACCINATION	1 DOSE	Yes	N/A
			22DEC2014(50)	22DEC2014(50)	PREVENAR 13	ANTIINFECTIVES FOR SYSTEMIC USE	PNEUMOCOCCAL VACCINE	UNK	UNK	IM	VACCINATION	1 DOSE	Yes	N/A
			19JAN2015(78)	19JAN2015(78)	HEXYON	ANTIINFECTIVES FOR SYSTEMIC USE	BACTERIAL AND VIRAL VACCINES, COMBINED	UNK	UNK	IM	VACCINATION	1 DOSE	Yes	N/A
			19JAN2015(78)	19JAN2015(78)	PREVENAR 13	ANTIINFECTIVES FOR SYSTEMIC USE	PNEUMOCOCCAL VACCINE	UNK	UNK	IM	VACCINATION	1 DOSE	Yes	N/A
			24FEB2015(114)	24FEB2015(114)	HEXYON	ANTIINFECTIVES FOR SYSTEMIC USE	BACTERIAL AND VIRAL VACCINES, COMBINED	UNK	UNK	IM	VACCINATION	1 DOSE	Yes	N/A
			24FEB2015(114)	24FEB2015(114)	PREVENAR 13	ANTIINFECTIVES FOR SYSTEMIC USE	PNEUMOCOCCAL VACCINE	UNK	UNK	IM	VACCINATION	1 DOSE	Yes	N/A
			19OCT2015(351)	19OCT2015(351)	PRIORIX	ANTIINFECTIVES FOR SYSTEMIC USE	MEASLES MUMPS & RUBELLA LIVE ATTENUATED (FREE	N/A	N/A	SUBCUTANEOUSLY	VACCINATION	ONCE	Yes	N/A
			19OCT2015(351)	19OCT2015(351)	VARILRIX	ANTIINFECTIVES FOR SYSTEMIC USE	VARICELLA ZOSTER VACCINE	N/A	N/A	SUBCUTANEOUS	VACCINATION	ONCE	Yes	N/A
			05NOV2015(368)	05NOV2015(368)	MENJUGATE	ANTIINFECTIVES FOR SYSTEMIC USE	MENINGOCOCCAL VACCINE	N/A	N/A	INTRAMUSCULARLY	VACCINATION	ONCE	Yes	N/A

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Listing 16.2.4.3 Concomitant Medications

Cohort	Patient ID	Gender	Start Date(Day)	Stop Date(Day)	Medication	ATC1 Name	Preferred Term	Dose	Unit	Route	Indication	Regimen	TE?	AE #
Cohort 2	3063-003	M	UK/UNK/UNK	UK/UNK/UNK	PARACETAMOL	NERVOUS SYSTEM	PARACETAMOL	UNK	UNK	P.O.	PNEUMONIA WITH BRONCHIAL SPASM	UNK		08
			25NOV2014(-1)	25NOV2014(-1)	PIRITRAMIDE	NERVOUS SYSTEM	PIRITRAMIDE	0.25	MG	IV	ANALGESIA, SEDATION	1 DOSE		N/A
			25NOV2014(-1)	11DEC2014(15)	SODIUM CHLORIDE	ALIMENTARY TRACT AND METABOLISM	SODIUM CHLORIDE	0.9	%	IV	TO KEEP CENTRAL LINE OPEN	CONTINUOUS INFUSION		N/A
			25NOV2014(-1)	12DEC2014(16)	NYSTATIN	ALIMENTARY TRACT AND METABOLISM	NYSTATIN	1	ML	ORL	THERAPY OF ORAL THRUSH	4X DAILY		03
			25NOV2014(-1)	12DEC2014(16)	GLUCOSE	BLOOD AND BLOOD FORMING ORGANS	GLUCOSE	20	%	ORL	SEDATION	PRN		N/A
			27NOV2014(1)	Cont.	SODIUM FLUORIDE COLECALCIFEROL	ALIMENTARY TRACT AND METABOLISM	SODIUM FLUORIDE W/VITAMINS NOS	500	I.U.	ORL	PREVENTION OF RICKETS AND CARIES	DAILY	Yes	N/A
			27NOV2014(1)	27NOV2014(1)	ESKETAMINE	NERVOUS SYSTEM	ESKETAMINE	3	MG	IV	SEDATION	1 DOSE	Yes	N/A
			27NOV2014(1)	27NOV2014(1)	MIDAZOLAM	NERVOUS SYSTEM	MIDAZOLAM	0.3	MG	IV	SEDATION	1 DOSE	Yes	N/A
			27NOV2014(1)	28NOV2014(2)	GLUCOSE	BLOOD AND BLOOD FORMING ORGANS	GLUCOSE	10	%	IV	LONG RECOVERY AFTER SEDATION	CONTINUOUS INFUSION	Yes	N/A
			11DEC2014(15)	11DEC2014(15)	PIRITRAMIDE	NERVOUS SYSTEM	PIRITRAMIDE	0.3	MG	IV	ANALGESIA, SEDATION	1 DOSE	Yes	N/A
			25JAN2015(60)	26JAN2015(61)	ADRENALINE	ALIMENTARY TRACT AND METABOLISM	EPINEPHRINE	3	%	INHALATIVE	BRONCHIOLITIS	EVERY 5 HOURS	Yes	05
			26JAN2015(61)	26JAN2015(61)	HYPERTONIC SALINE SOLUTION	ALIMENTARY TRACT AND METABOLISM	SODIUM CHLORIDE	3	%	INHALATIVE	BRONCHIOLITIS	EVERY 5 HOURS	Yes	05
			27JAN2015(62)	27JAN2015(62)	HYPERTONIC SALINE SOLUTION	ALIMENTARY TRACT AND METABOLISM	SODIUM CHLORIDE	3	%	INHALATIVE	BRONCHIOLITIS	EVERY 6 HOURS	Yes	05

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Cohort	Patient ID	Gender	Start Date(Day)	Stop Date(Day)	Medication	ATC1 Name	Preferred Term	Dose	Unit	Route	Indication	Regimen	TE?	AE #
Cohort 2	3063-003	M	28JAN2015(63)	31JAN2015(66)	HYPERTONIC SALINE SOLUTION	ALIMENTARY TRACT AND METABOLISM	SODIUM CHLORIDE	3	%	INHALATIVE	BRONCHIOLITIS	3 TIMES DAILY	Yes	05
			09FEB2015(75)	09FEB2015(75)	VACCINE AGAINST DIPHTHERIA	ANTIINFECTIVES FOR SYSTEMIC USE	DIPHTHERIA VACCINE	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A
			09FEB2015(75)	09FEB2015(75)	VACCINE AGAINST HIB	ANTIINFECTIVES FOR SYSTEMIC USE	HAEMOPHILUS INFLUENZA TYPE B VACCINE	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A
			09FEB2015(75)	09FEB2015(75)	VACCINE AGAINST HEPATITIS B	ANTIINFECTIVES FOR SYSTEMIC USE	HEPATITIS B VACCINE	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A
			09FEB2015(75)	09FEB2015(75)	VACCINE AGAINST WHOOPING COUGH	ANTIINFECTIVES FOR SYSTEMIC USE	PERTUSSIS VACCINE	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A
			09FEB2015(75)	09FEB2015(75)	VACCINE AGAINST PNEUMOCOCCI	ANTIINFECTIVES FOR SYSTEMIC USE	PNEUMOCOCCAL VACCINE	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A
			09FEB2015(75)	09FEB2015(75)	VACCINE AGAINST POLYOMYELITIS	ANTIINFECTIVES FOR SYSTEMIC USE	POLIOMYELITIS VACCINES	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A
			09FEB2015(75)	09FEB2015(75)	VACCINE AGAINST TETANUS	ANTIINFECTIVES FOR SYSTEMIC USE	TETANUS VACCINE	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A
			10APR2015(135)	15APR2015(140)	AMOXICILLIN	ANTIINFECTIVES FOR SYSTEMIC USE	AMOXICILLIN	80	MG/ML	ORL	BRONCHOPNEUMONIA	3 X DAILY	Yes	07
			10APR2015(135)	15APR2015(140)	CLAVULANIC ACID	ANTIINFECTIVES FOR SYSTEMIC USE	AMOXICILLIN W/CLAVULANATE POTASSIUM	11.4	MG/ML	ORL	BRONCHOPNEUMONIA WITH BACTEREREMIA	3 X DAILY	Yes	07
			10APR2015(135)	17APR2015(142)	IPRATROPIUM BROMIDE	CARDIOVASCULAR SYSTEM	IPRATROPIUM BROMIDE	125	MCG	INHALATIVE	BRONCHOPNEUMONIA	2-3 X DAILY	Yes	07
			10APR2015(135)	17APR2015(142)	SALBUTAMOL	RESPIRATORY SYSTEM	SALBUTAMOL	0.75	MG	INHALATIVE	BRONCHOPNEUMONIA	3-6 X DAILY	Yes	07

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Cohort	Patient ID	Gender	Start Date(Day)	Stop Date(Day)	Medication	ATC1 Name	Preferred Term	Dose	Unit	Route	Indication	Regimen	TE?	AE #
Cohort 2	3063-003	M	13APR2015(138)	15APR2015(140)	BETAMETASONE	ALIMENTARY TRACT AND METABOLISM	BETAMETHASONE	0.5	MG	ORL	BRONCHOPNEUMONIA	2 X DAILY	Yes	07
			15APR2015(140)	21APR2015(146)	CEFTAZIDIME	ANTIINFECTIVES FOR SYSTEMIC USE	CEFTAZIDIME	200	MG	IV	BRONCHOPNEUMONIA	3 X DAILY	Yes	07
			16APR2015(141)	18APR2015(143)	BETAMETASONE	ALIMENTARY TRACT AND METABOLISM	BETAMETHASONE	0.5	MG	ORL	BRONCHOPNEUMONIA	DAILY	Yes	07
			08MAY2015(163)	08MAY2015(163)	VACCINE AGAINST DIPHTHERIA	ANTIINFECTIVES FOR SYSTEMIC USE	DIPHTHERIA VACCINE	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A
			08MAY2015(163)	08MAY2015(163)	VACCINE AGAINST HIB	ANTIINFECTIVES FOR SYSTEMIC USE	HAEMOPHILUS INFLUENZA TYPE B VACCINE	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A
			08MAY2015(163)	08MAY2015(163)	VACCINE AGAINST HEPATITIS B	ANTIINFECTIVES FOR SYSTEMIC USE	HEPATITIS B VACCINE	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A
			08MAY2015(163)	08MAY2015(163)	VACCINE AGAINST WHOOPING COUGH	ANTIINFECTIVES FOR SYSTEMIC USE	PERTUSSIS VACCINE	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A
			08MAY2015(163)	08MAY2015(163)	VACCINE AGAINST PNEUMOCOCCI	ANTIINFECTIVES FOR SYSTEMIC USE	PNEUMOCOCCAL VACCINE	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A
			08MAY2015(163)	08MAY2015(163)	VACCINE AGAINST POLYOMYELITIS	ANTIINFECTIVES FOR SYSTEMIC USE	POLIOMYELITIS VACCINES	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A
			08MAY2015(163)	08MAY2015(163)	VACCINE AGAINST TETANUS	ANTIINFECTIVES FOR SYSTEMIC USE	TETANUS VACCINE	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A
			19JUN2015(205)	UK/UNK/UNK	IPRATROPIUM BROMIDE	CARDIOVASCULAR SYSTEM	IPRATROPIUM BROMIDE	UNK	UNK	INHALATION	PNEUMONIA WITH BRONCHIAL SPASM	3 X DAILY	Yes	08

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Cohort	Patient ID	Gender	Start Date(Day)	Stop Date(Day)	Medication	ATC1 Name	Preferred Term	Dose	Unit	Route	Indication	Regimen	TE?	AE #
Cohort 2	3063-003	M	19JUN2015(205)	UK/UNK/UNK	SALBUTAMOL	RESPIRATORY SYSTEM	SALBUTAMOL	0.75	MG	INHALATION	PNEUMONIA WITH BRONCHIAL SPASM	3 X DAILY	Yes	08
			19JUN2015(205)	20JUN2015(206)	GLUCOSE-ELECTROLYTE SOLUTION	BLOOD AND BLOOD FORMING ORGANS	ELECTROLYTES NOS W/GLUCOSE	UNK	UNK	I.V.	PNEUMONIA WITH BRONCHIAL SPASM	UNK	Yes	08
			19JUN2015(205)	21JUN2015(207)	OXYGEN	ALIMENTARY TRACT AND METABOLISM	OXYGEN	UNK	UNK	INHALATION	PNEUMONIA WITH BRONCHIAL SPASM	UNK	Yes	08
			19JUN2015(205)	22JUN2015(208)	BETAMETASONE	ALIMENTARY TRACT AND METABOLISM	BETAMETHASONE	0.5	MG	P.O.	PNEUMONIA WITH BRONCHIAL SPASM	1 X DAILY	Yes	08
			19JUN2015(205)	22JUN2015(208)	AMOXICILLIN	ANTIINFECTIVES FOR SYSTEMIC USE	AMOXICILLIN	125	MG	P.O.	PNEUMONIA WITH BRONCHIAL SPASM	3 X DAILY	Yes	08
			19JUN2015(205)	22JUN2015(208)	CLAVULANIC ACID	ANTIINFECTIVES FOR SYSTEMIC USE	AMOXICILLIN W/CLAVULANATE POTASSIUM	UNK	UNK	P.O.	PNEUMONIA WITH BRONCHIAL SPASM	3 X DAILY	Yes	08
			26NOV2015(365)	26NOV2015(365)	VACCINE AGAINST DIPHTHERIA	ANTIINFECTIVES FOR SYSTEMIC USE	DIPHTHERIA VACCINE	N/A	N/A	UNK	VACCINATION	1 DOSE	Yes	N/A
			26NOV2015(365)	26NOV2015(365)	VACCINE AGAINST HIB	ANTIINFECTIVES FOR SYSTEMIC USE	HAEMOPHILUS INFLUENZA TYPE B VACCINE	N/A	N/A	UNK	VACCINATION	1 DOSE	Yes	N/A
			26NOV2015(365)	26NOV2015(365)	VACCINE AGAINST HEPATITIS B	ANTIINFECTIVES FOR SYSTEMIC USE	HEPATITIS B VACCINE	N/A	N/A	UNK	VACCINATION	1 DOSE	Yes	N/A
			26NOV2015(365)	26NOV2015(365)	VACCINE AGAINST WHOOPING COUGH	ANTIINFECTIVES FOR SYSTEMIC USE	PERTUSSIS VACCINE	N/A	N/A	UNK	VACCINATION	1 DOSE	Yes	N/A

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Cohort 2	3063-003	M	26NOV2015(365)	26NOV2015(365)	VACCINE AGAINST PNEUMOCOCCI	ANTIINFECTIVES FOR SYSTEMIC USE	PNEUMOCOCCAL VACCINE	N/A	N/A	UNK	VACCINATION	1 DOSE	Yes	N/A
			26NOV2015(365)	26NOV2015(365)	VACCINE AGAINST POLIOMYELITIS	ANTIINFECTIVES FOR SYSTEMIC USE	POLIO VACCINE	N/A	N/A	UNK	VACCINATION	1 DOSE	Yes	N/A
			26NOV2015(365)	26NOV2015(365)	VACCINE AGAINST TETANUS	ANTIINFECTIVES FOR SYSTEMIC USE	TETANUS VACCINE	N/A	N/A	UNK	VACCINATION	1 DOSE	Yes	N/A
Cohort 2	3063-004	M	02JAN2015(-3)	02JAN2015(-3)	PHYTOMENANDION	BLOOD AND BLOOD FORMING ORGANS	PHYTOMENADIONE	2	MG	ORL	PREVENTION OF BLEEDING IN NEWBORNS	1 DOSE		N/A
			05JAN2015(0)	05JAN2015(0)	SODIUM CHLORIDE	ALIMENTARY TRACT AND METABOLISM	SODIUM CHLORIDE	0.9	%	IV	TO KEEP CENTRAL LINE OPEN	CONTINUOUS INFUSION	Yes	N/A
			05JAN2015(0)	05JAN2015(0)	GLUCOSE	BLOOD AND BLOOD FORMING ORGANS	GLUCOSE	10	%	IV	LONG RECOVERY AFTER SEDATION	CONTINUOUS INFUSION	Yes	N/A
			05JAN2015(0)	05JAN2015(0)	ESKETAMINE	NERVOUS SYSTEM	ESKETAMINE	2.5	MG	IV	SEDATION	2 DOSES	Yes	N/A
			05JAN2015(0)	05JAN2015(0)	MIDAZOLAM	NERVOUS SYSTEM	MIDAZOLAM	0.4	MG	IV	SEDATION	1 DOSE	Yes	N/A
			06JAN2015(1)	06JAN2015(1)	PIRITRAMIDE	NERVOUS SYSTEM	PIRITRAMIDE	0.3	MG	IV	ANALGESIA, SEDATION	1 DOSE	Yes	N/A
			10JAN2015(5)	Cont.	VITAMIN D	ALIMENTARY TRACT AND METABOLISM	ERGOCALCIFEROL	500	I.E.	ORALLY	RICKETS	DAILY	Yes	N/A
			10JAN2015(5)	Cont.	VITAMIN D	ALIMENTARY TRACT AND METABOLISM	ERGOCALCIFEROL	500	I.E.	ORL	RICKETS	DAILY	Yes	N/A
			10JAN2015(5)	Cont.	SODIUMFLUORIDE-COLECALCIFEROL	ALIMENTARY TRACT AND METABOLISM	SODIUM FLUORIDE W/VITAMINS NOS	500	I.U.	ORL	PREVENTION OF RICKETS AND CARIES	DAILY	Yes	N/A
			20JAN2015(15)	20JAN2015(15)	PIRITRAMIDE	NERVOUS SYSTEM	PIRITRAMIDE	0.3	MG	IV	ANALGESIA, SEDATION	1 DOSE	Yes	N/A

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Listing 16.2.4.3 Concomitant Medications

Cohort	Patient ID	Gender	Start Date(Day)	Stop Date(Day)	Medication	ATC1 Name	Preferred Term	Dose	Unit	Route	Indication	Regimen	TE?	AE #
Cohort 2	3063-004	M	11FEB2015(37)	11FEB2015(37)	PHYTOMENANDION	BLOOD AND BLOOD FORMING ORGANS	PHYTOMENADIONE	2	MG	ORL	PREVENTION OF BLEEDING IN NEWBORNS	1 DOSE	Yes	N/A
			30MAR2015(84)	30MAR2015(84)	ROTATEQ	ANTIINFECTIVES FOR SYSTEMIC USE	ROTAVIRUS VACCINE	UNK	UNK	ORL	VACCINATION	1 DOSE	Yes	N/A
			21APR2015(106)	21APR2015(106)	INFANRIX HEXA	ANTIINFECTIVES FOR SYSTEMIC USE	INFANRIX HEXA	UNK	UNK	IM	VACCINATION	1 DOSE	Yes	N/A
			21APR2015(106)	21APR2015(106)	PREVENAR 13	ANTIINFECTIVES FOR SYSTEMIC USE	PNEUMOCOCCAL VACCINE	UNK	UNK	IM	VACCINATION	1 DOSE	Yes	N/A
			21APR2015(106)	21APR2015(106)	ROTATEQ	ANTIINFECTIVES FOR SYSTEMIC USE	ROTAVIRUS VACCINE	UNK	UNK	ORL	VACCINATION	1 DOSE	Yes	N/A
			19MAY2015(134)	19MAY2015(134)	INFANRIX HEXA	ANTIINFECTIVES FOR SYSTEMIC USE	INFANRIX HEXA	UNK	UNK	IM	VACCINATION	1 DOSE	Yes	N/A
			19MAY2015(134)	19MAY2015(134)	PREVENAR 13	ANTIINFECTIVES FOR SYSTEMIC USE	PNEUMOCOCCAL VACCINE	UNK	UNK	IM	VACCINATION	1 DOSE	Yes	N/A
			19MAY2015(134)	19MAY2015(134)	ROTATEQ	ANTIINFECTIVES FOR SYSTEMIC USE	ROTAVIRUS VACCINE	UNK	UNK	ORL	VACCINATION	1 DOSE	Yes	N/A
			22JUN2015(168)	22JUN2015(168)	INFANRIX HEXA	ANTIINFECTIVES FOR SYSTEMIC USE	INFANRIX HEXA	UNK	UNK	IM	VACCINATION	1 DOSE	Yes	N/A
			22JUN2015(168)	22JUN2015(168)	PREVENAR 13	ANTIINFECTIVES FOR SYSTEMIC USE	PNEUMOCOCCAL VACCINE	UNK	UNK	IM	VACCINATION	1 DOSE	Yes	N/A
			13NOV2015(312)	15NOV2015(314)	PARACETAMOL	NERVOUS SYSTEM	PARACETAMOL	125	MG	RECTAL	FEVER	TWICE	Yes	13
Cohort 3	1068-002	M	25FEB2015(-2)	25FEB2015(-2)	1% LIDOCAINE BUFFERED 1:10	CARDIOVASCULAR SYSTEM	LIDOCAINE	0.15	ML	SQ	PAIN - PICC PLACEMENT	X1		N/A

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Listing 16.2.4.3 Concomitant Medications

Cohort	Patient ID	Gender	Start Date(Day)	Stop Date(Day)	Medication	ATC1 Name	Preferred Term	Dose	Unit	Route	Indication	Regimen	TE?	AE #
Cohort 3	1068-002	M	25FEB2015(-2)	05MAR2015(6)	NYSTATIN SOLUTION	ALIMENTARY TRACT AND METABOLISM	NYSTATIN	100,000	UNITS	PO	THRUSH	Q 6 HR		N/A
			25FEB2015(-2)	06MAR2015(7)	1/4 NS + HEPARIN 1000 UNITS/ML	BLOOD AND BLOOD FORMING ORGANS	HEPARIN SODIUM W/SODIUM CHLORIDE	1.0	ML/HOUR	IV	PICC LINE	CONTINUOUS		N/A
			25FEB2015(-2)	08MAR2015(9)	NYSTATIN CREAM	ALIMENTARY TRACT AND METABOLISM	NYSTATIN	1	APPLICATION	TOPICAL	DIAPER RASH	Q 6 HR		N/A
			26FEB2015(-1)	26FEB2015(-1)	1% LIDOCAINE	CARDIOVASCULAR SYSTEM	LIDOCAINE	1.1	ML	SQ	PAIN - SKIN BIOPSY	X1		N/A
			26FEB2015(-1)	13MAR2015(14)	HEPARIN FLUSH	BLOOD AND BLOOD FORMING ORGANS	HEPARIN	0.5	ML	IV	PICC LINE	BID		N/A
			27FEB2015(0)	10MAR2015(11)	CHOLECALCIFERAL (VITAMIN D3)	ALIMENTARY TRACT AND METABOLISM	COLECALCIFEROL	200	IU	PO	NUTRITION	QD	Yes	N/A
			28FEB2015(1)	28FEB2015(1)	1% LIDOCAINE	CARDIOVASCULAR SYSTEM	LIDOCAINE	1.0	ML	SQ	PAIN - SKIN BIOPSY	X1	Yes	N/A
			03MAR2015(4)	10MAR2015(11)	BACITRACIN POLYMYXIN B OINTMENT	DERMATOLOGICALS	BACITRACIN W/POLYMYXIN B	1	APPLICATION	TOPICAL	LEFT THIGH BIOPSY SITE	QID	Yes	2
			05MAR2015(6)	05MAR2015(6)	GENTIAN VIOLET 1% SOLUTION	DERMATOLOGICALS	METHYLROSANILINIUM CHLORIDE	1	ML	PO	THRUSH	X1	Yes	N/A
			05MAR2015(6)	08MAR2015(9)	TRIMETHOPRIM POLYMYXIN B OPTHALMIC SOLUTION	SENSORY ORGANS	POLYMYXIN B W/TRIMETHOPRIM	1	DROP	EACH EYE	EYE DRAINAGE	Q 3 HOURS	Yes	N/A
			06MAR2015(7)	13MAR2015(14)	1/4 NS + HEPARIN 500 UNITS/ML	BLOOD AND BLOOD FORMING ORGANS	HEPARIN SODIUM W/SODIUM CHLORIDE	5.0	ML/HOUR	IV	PICC LINE	CONTINUOUS	Yes	1
			08MAR2015(9)	14MAR2015(15)	ERYTHROMYCIN 0.5% OPHTHALMIC OINTMENT	DERMATOLOGICALS	ERYTHROMYCIN	1	APPLICATION	EACH EYE	EYE DRAINAGE	Q 6 HOURS	Yes	N/A
			09MAR2015(10)	18MAR2015(19)	AQUAPHOR TOPICAL CREAM	DERMATOLOGICALS	AQUAPHOR /01181901/	1	APPLICATION	TOPICAL	DRY SKIN	Q 3 HOURS PRN	Yes	N/A

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Listing 16.2.4.3 Concomitant Medications

Cohort	Patient ID	Gender	Start Date(Day)	Stop Date(Day)	Medication	ATC1 Name	Preferred Term	Dose	Unit	Route	Indication	Regimen	TE?	AE #
Cohort 3	1068-002	M	11MAR2015(12)	18MAR2015(19)	TRIPLE PASTE	DERMATOLOGICALS	ZINC OXIDE	1	APPLICATION	TOPICAL	DIAPER RASH	PRN	Yes	N/A
			14MAR2015(15)	14MAR2015(15)	1% LIDOCAINE	CARDIOVASCULAR SYSTEM	LIDOCAINE	1.0	ML	SQ	PAIN - SKIN BIOPSY	X1	Yes	N/A
			19MAR2015(20)	Cont.	AQUAPHOR TOPICAL CREAM	DERMATOLOGICALS	AQUAPHOR /01181901/	1	APPLICATION	TOPICAL	DRY SKIN	PRN	Yes	N/A
			19MAR2015(20)	Cont.	AQUAPHOR TOPICAL CREAM	DERMATOLOGICALS	AQUAPHOR /01181901/	1	APPLICATION	TOPICAL	DRY SKIN	PRN	Yes	N/A
			19MAR2015(20)	20MAR2015(21)	TRIPLE PASTE	DERMATOLOGICALS	ZINC OXIDE	1	APPLICATION	TOPICAL	DIAPER RASH	PRN	Yes	N/A
			19MAR2015(20)	23MAR2015(24)	NYSTATIN CREAM	ALIMENTARY TRACT AND METABOLISM	NYSTATIN	1	APPLICATION	TOPICAL	DIAPER RASH	Q 6 HOURS	Yes	N/A
			19MAR2015(20)	23MAR2015(24)	BACITRACIN POLYMYXIN B OPHTHALMIC OINTMENT	DERMATOLOGICALS	BACITRACIN W/POLYMYXIN B	1	APPLICATION	RIGHT EYE	EYE INFECTION	Q 12 HOURS	Yes	N/A
			20MAR2015(21)	30JUN2015(123)	CHOLECALCIFEROL VITAMIN D3	ALIMENTARY TRACT AND METABOLISM	COLECALCIFEROL	200	IU	PO	NUTRITION	QD	Yes	N/A
			23MAR2015(24)	20APR2015(52)	LITTLE REMEDIES SALINE SPRAY/DROPS	RESPIRATORY SYSTEM	SALINE /01783401/	2-4	DROPS	EACH NOSTRIL	CONGESTION	PRN	Yes	N/A
			12APR2015(44)	20APR2015(52)	DESITIN CREAM	DERMATOLOGICALS	DESITIN /01754701/	1	APPLICATION	TOPICAL	DIAPER RASH	PRN	Yes	N/A
			15APR2015(47)	15APR2015(47)	DIPHTHERIA VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	DIPHTHERIA VACCINE	N/A	N/A	IM	ROUTINE VACCINATION	ONCE	Yes	N/A
			15APR2015(47)	15APR2015(47)	HAEMOPHILUS INFLUENZAE TYPE B VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	HAEMOPHILUS INFLUENZA TYPE B VACCINE	N/A	N/A	IM	ROUTINE VACCINATION	ONCE	Yes	N/A
			15APR2015(47)	15APR2015(47)	HEPATITUS B VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	HEPATITIS B VACCINE	0.5	ML	IM	ROUTINE VACCINATION	ONCE	Yes	N/A

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Listing 16.2.4.3 Concomitant Medications

Cohort	Patient ID	Gender	Start Date(Day)	Stop Date(Day)	Medication	ATC1 Name	Preferred Term	Dose	Unit	Route	Indication	Regimen	TE?	AE #
Cohort 3	1068-002	M	15APR2015(47)	15APR2015(47)	PERTUSSIS VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	PERTUSSIS VACCINE	N/A	N/A	IM	ROUTINE VACCINATION	ONCE	Yes	N/A
			15APR2015(47)	15APR2015(47)	PCV13 PNEUMOCOCCAL VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	PNEUMOCOCCAL VACCINE	0.5	ML	IM	ROUTINE VACCINATION	ONCE	Yes	N/A
			15APR2015(47)	15APR2015(47)	POLIO VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	POLIO VACCINE	N/A	N/A	IM	ROUTINE VACCINATION	ONCE	Yes	N/A
			15APR2015(47)	15APR2015(47)	TETANUS VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	TETANUS VACCINE	N/A	N/A	IM	ROUTINE VACCINATION	ONCE	Yes	N/A
			20APR2015(52)	30JUN2015(123)	HARMON FACE VALUES SALINE NASAL SPRAY 0.65% SODIUM CHLORIDE	ALIMENTARY TRACT AND METABOLISM	SODIUM CHLORIDE	1	SPRAY	EACH NOSTRIL	NASAL CONGESTION	PRN	Yes	N/A
			15JUN2015(108)	15JUN2015(108)	PNEUMOCOCCAL VACCINE 13-VALENT	ANTIINFECTIVES FOR SYSTEMIC USE	PNEUMOCOCCAL VACCINE	N/A	N/A	IM	ROUTINE VACCINATION	ONCE	Yes	N/A
			20JUN2015(113)	Cont.	NEOSPORIN	DERMATOLOGICALS	NEOSPORIN /00130801/	1	APPLICATION	TOPICAL	SCRATCHES	PRN	Yes	N/A
			20JUN2015(113)	Cont.	NEOSPORIN	DERMATOLOGICALS	NEOSPORIN /00130801/	1	APPLICATION	TOPICAL	SCRATCHES	PRN	Yes	N/A
			29JUN2015(122)	29JUN2015(122)	DIPHTHERIA VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	DIPHTHERIA VACCINE	N/A	N/A	IM	ROUTINE VACCINATION	ONCE	Yes	N/A
			29JUN2015(122)	29JUN2015(122)	HAEMOPHILUS INFLUENZAE TYPE B VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	HAEMOPHILUS INFLUENZA TYPE B VACCINE	N/A	N/A	IM	ROUTINE VACCINATION	ONCE	Yes	N/A
			29JUN2015(122)	29JUN2015(122)	HAEMOPHILUS INFLUENZAE TYPE B VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	HAEMOPHILUS INFLUENZA TYPE B VACCINE	N/A	N/A	IM	ROUTINE VACCINATION	ONCE	Yes	N/A
			29JUN2015(122)	29JUN2015(122)	PERTUSSIS VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	PERTUSSIS VACCINE	N/A	N/A	IM	ROUTINE VACCINATION	ONCE	Yes	N/A

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Listing 16.2.4.3 Concomitant Medications

Cohort	Patient ID	Gender	Start Date(Day)	Stop Date(Day)	Medication	ATC1 Name	Preferred Term	Dose	Unit	Route	Indication	Regimen	TE?	AE #
Cohort 3	1068-002	M	29JUN2015(122)	29JUN2015(122)	POLIO VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	POLIO VACCINE	N/A	N/A	IM	ROUTINE VACCINATION	ONCE	Yes	N/A
			29JUN2015(122)	29JUN2015(122)	POLIO VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	POLIO VACCINE	N/A	N/A	IM	ROUTINE VACCINATION	ONCE	Yes	N/A
			29JUN2015(122)	29JUN2015(122)	TETANUS VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	TETANUS VACCINE	N/A	N/A	IM	ROUTINE VACCINATION	ONCE	Yes	N/A
			01AUG2015(155)	Cont.	DESITIN CREAM	DERMATOLOGICALS	DESITIN /01754701/	1	APPLICATION	TOPICAL	DIAPER RASH	PRN	Yes	N/A
			01AUG2015(155)	Cont.	DESITIN CREAM	DERMATOLOGICALS	DESITIN /01754701/	1	APPLICATION	TOPICAL	DIAPER RASH	PRN	Yes	N/A
			10AUG2015(164)	10AUG2015(164)	DIPHTHERIA VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	DIPHTHERIA VACCINE	N/A	N/A	IM	ROUTINE VACCINATION	ONCE	Yes	N/A
			10AUG2015(164)	10AUG2015(164)	HAEMOPHILUS INFLUENZAE TYPE B VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	HAEMOPHILUS INFLUENZA TYPE B VACCINE	N/A	N/A	IM	ROUTINE VACCINATION	ONCE	Yes	N/A
			10AUG2015(164)	10AUG2015(164)	HEPATITIS B VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	HEPATITIS B VACCINE	0.5	ML	IM	ROUTINE VACCINATION	ONCE	Yes	N/A
			10AUG2015(164)	10AUG2015(164)	PERTUSSIS VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	PERTUSSIS VACCINE	N/A	N/A	IM	ROUTINE VACCINATION	ONCE	Yes	N/A
			10AUG2015(164)	10AUG2015(164)	PREVNAR-13 VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	PNEUMOCOCCAL VACCINE	0.5	ML	IM	ROUTINE VACCINATION	ONCE	Yes	N/A
			10AUG2015(164)	10AUG2015(164)	INACTIVATED POLIO VIRUS VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	POLIO VACCINE	N/A	N/A	IM	ROUTINE VACCINATION	ONCE	Yes	N/A
			10AUG2015(164)	10AUG2015(164)	TETANUS VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	TETANUS VACCINE	N/A	N/A	IM	ROUTINE VACCINATION	ONCE	Yes	N/A

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Listing 16.2.4.3 Concomitant Medications

Cohort	Patient ID	Gender	Start Date(Day)	Stop Date(Day)	Medication	ATC1 Name	Preferred Term	Dose	Unit	Route	Indication	Regimen	TE?	AE #
Cohort 3	3064-002	M	30MAR2015(-10)	30MAR2015(-10)	VITAMIN K	BLOOD AND BLOOD FORMING ORGANS	PHYTOMENADIONE	2	MG	IM	PREVENTION	STAT		N/A
			06APR2015(-3)	Cont.	HYDROMOL	DERMATOLOGICALS	HYDROMOL /00906601/	0.5	CAPFUL	ADD TO BATH	PREVENT DRY SKIN	AS REQUIRED		N/A
			07APR2015(-2)	Cont.	SALINE NOSE DROPS	RESPIRATORY SYSTEM	SALINE /01783401/	1	DROP	NOSTRIL	NASAL CONGESTION	PRN		N/A
			07APR2015(-2)	07APR2015(-2)	LIGNOCAINE 1%	CARDIOVASCULAR SYSTEM	LIDOCAINE	2	MLS	S/C	PREVENT PAIN	STAT		N/A
			10APR2015(1)	10APR2015(1)	LIGNOCAINE 1%	CARDIOVASCULAR SYSTEM	LIDOCAINE	2	MLS	S/C	PREVENT PAIN	STAT	Yes	N/A
			10APR2015(1)	10MAY2015(31)	EMLA	NERVOUS SYSTEM	EMLA /00675501/	5%	1 BLOB	TOPICAL	PREVENT PAIN	PRN	Yes	N/A
			21APR2015(12)	21APR2015(12)	PARACETAMOL	NERVOUS SYSTEM	PARACETAMOL	30	MG	PO	UNSETTLED	ONCE	Yes	18
			24APR2015(15)	24APR2015(15)	LIGNOCAINE 0.5%	CARDIOVASCULAR SYSTEM	LIDOCAINE	2	ML	S/C	PREVENT PAIN	STAT	Yes	N/A
			12MAY2015(33)	Cont.	DIPROBASE CREAM	DERMATOLOGICALS	DIPROBASE /01210201/	1	BLOB	TOPICAL	PREVENT DRY SKIN	QDS	Yes	N/A
			26MAY2015(47)	26MAY2015(47)	DIPTHERIA VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	DIPHTHERIA VACCINE	0.5	ML	IM	CHILDHOOD IMMUNISATION	STAT	Yes	N/A
			26MAY2015(47)	26MAY2015(47)	PERTUSSIS VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	PERTUSSIS VACCINE	0.5	MLS	IM	CHILDHOOD IMMUNISATION	STAT	Yes	N/A
			26MAY2015(47)	26MAY2015(47)	POLIO	ANTIINFECTIVES FOR SYSTEMIC USE	POLIO VACCINE	0.5	MLS	IM	CHILDHOOD IMMUNISATION	STAT	Yes	N/A
			26MAY2015(47)	26MAY2015(47)	TETANUS VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	TETANUS VACCINE	0.5	MLS	IM	CHILDHOOD IMMUNISATION	STAT	Yes	N/A
			26MAY2015(47)	26MAY2015(47)	HAEMOPHILUS INFLUENZA B	RESPIRATORY SYSTEM	HAEMOPHILUS INFLUENZAE	0.5	MLS	IM	CHILDHOOD IMMUNISATION	STAT	Yes	N/A
			23JUN2015(75)	23JUN2015(75)	DIPTHERIA VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	DIPHTHERIA VACCINE	0.5	MLS	IM	CHILDHOOD IMMUNISATION	STAT	Yes	N/A

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Cohort	Patient ID	Gender	Start Date(Day)	Stop Date(Day)	Medication	ATC1 Name	Preferred Term	Dose	Unit	Route	Indication	Regimen	TE?	AE #
Cohort 3	3064-002	M	23JUN2015(75)	23JUN2015(75)	MENINGITIS C VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	MENINGOCOCCAL VACCINE	0.5	MLS	IM	CHILDHOOD IMMUNISATION	STAT	Yes	N/A
			23JUN2015(75)	23JUN2015(75)	PERTUSSIS VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	PERTUSSIS VACCINE	0.5	MLS	IM	CHILDHOOD IMMUNISATION	STAT	Yes	N/A
			23JUN2015(75)	23JUN2015(75)	POLIO	ANTIINFECTIVES FOR SYSTEMIC USE	POLIO VACCINE	0.5	MLS	IM	CHILDHOOD IMMUNISATION	STAT	Yes	N/A
			23JUN2015(75)	23JUN2015(75)	TETANUS VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	TETANUS VACCINE	0.5	MLS	IM	CHILDHOOD IMMUNISATION	STAT	Yes	N/A
			23JUN2015(75)	23JUN2015(75)	HAEMOPHILUS INFLUENZA B	RESPIRATORY SYSTEM	HAEMOPHILUS INFLUENZAE	0.5	MLS	IM	CHILDHOOD IMMUNISATION	STAT	Yes	N/A
			30JUN2015(82)	06JUL2015(88)	CEFUROXIME	ANTIINFECTIVES FOR SYSTEMIC USE	CEFUROXIME	100/KG	MG	1V	CHEST INFECTION	TDS	Yes	03
			28JUL2015(110)	28JUL2015(110)	DIPTHERIA VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	DIPHTHERIA VACCINE	0.5	MLS	IM	CHILDHOOD IMMUNISATION	STAT	Yes	N/A
			28JUL2015(110)	28JUL2015(110)	PERTUSSIS VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	PERTUSSIS VACCINE	0.5	MLS	IM	CHILDHOOD IMMUNISATION	STAT	Yes	N/A
			28JUL2015(110)	28JUL2015(110)	POLIO	ANTIINFECTIVES FOR SYSTEMIC USE	POLIO VACCINE	0.5	MLS	IM	CHILDHOOD IMMUNISATION	STAT	Yes	N/A
			28JUL2015(110)	28JUL2015(110)	TETANUS VACCINE	ANTIINFECTIVES FOR SYSTEMIC USE	TETANUS VACCINE	0.5	MLS	IM	CHILDHOOD IMMUNISATION	STAT	Yes	N/A
			28JUL2015(110)	28JUL2015(110)	HAEMOPHILUS INFLUENZA B	RESPIRATORY SYSTEM	HAEMOPHILUS INFLUENZAE	0.5	MLS	IM	CHILDHOOD IMMUNISATION	STAT	Yes	N/A
			17AUG2015(130)	Cont.	CEFALEXIN	ANTIINFECTIVES FOR SYSTEMIC USE	CEFALEXIN	70	MG	PO	RESPIRATORY PROPHYLAXIS	OD	Yes	N/A

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Cohort	Patient ID	Gender	Start Date(Day)	Stop Date(Day)	Medication	ATC1 Name	Preferred Term	Dose	Unit	Route	Indication	Regimen	TE?	AE #
Cohort 3	3064-002	M	17AUG2015(130)	Cont.	NUTILIS CLEAR POWDER	VARIOUS	ALL OTHER NON-THERAPEUTIC PRODUCTS	2	SCOOPS	PO	FEED THICKENER	PRN	Yes	N/A
			15SEP2015(159)	Cont.	GLYCOPYRRONIUM BROMIDE	ALIMENTARY TRACT AND METABOLISM	GLYCOPYRRONIUM BROMIDE	280	MCG	PO	MINIMISE ORAL SECRETIONS	TDS	Yes	N/A
			16SEP2015(160)	Cont.	CAVILON	ALIMENTARY TRACT AND METABOLISM	DIMETICONE	1	ML	TOPICAL	MAINTAIN SKIN INTEGRITY	PRN	Yes	N/A
			16SEP2015(160)	Cont.	RANITIDINE	ALIMENTARY TRACT AND METABOLISM	RANITIDINE	3.75	MG	PO	PREVENT REFLUX	TDS	Yes	N/A
Siblings	1068-201	M	04MAY2013	Cont.	KROGER BRAND GUMMY MULTIVITAMIN	ALIMENTARY TRACT AND METABOLISM	MULTIVITAMINS	1	GUMMY	PO	NUTRITION	QD	Yes	N/A
	3063-202	M	09AUG2013	09AUG2013	VACCINE AGAINST DIPHTHERIA	ANTIINFECTIVES FOR SYSTEMIC USE	DIPHTHERIA VACCINE	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A
			09AUG2013	09AUG2013	VACCINE AGAINST HEPATITS B	ANTIINFECTIVES FOR SYSTEMIC USE	HEPATITIS B VACCINE	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A
			09AUG2013	09AUG2013	VACCINE AGAINST WHOOPING COUGH	ANTIINFECTIVES FOR SYSTEMIC USE	PERTUSSIS VACCINE	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A
			09AUG2013	09AUG2013	VACCINE AGAINST PNEUMOCOCCI	ANTIINFECTIVES FOR SYSTEMIC USE	PNEUMOCOCCAL VACCINE	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A
			09AUG2013	09AUG2013	VACCINE AGAINST POLIOMYELITIS	ANTIINFECTIVES FOR SYSTEMIC USE	POLIO VACCINE	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A
			09AUG2013	09AUG2013	VACCINE AGAINST TETANUS	ANTIINFECTIVES FOR SYSTEMIC USE	TETANUS VACCINE	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A

N/A = Not Applicable, Cont. = Continuing at end of study, TE (Treatment Emergent) = YES if the medication was started on Study Day 0 or later
* Treatment for the RSV infection in patient 3063-001 occurred at an outside hospital; not at the study research site.

Listing 16.2.4.3 Concomitant Medications

Cohort	Patient ID	Gender	Start Date(Day)	Stop Date(Day)	Medication	ATC1 Name	Preferred Term	Dose	Unit	Route	Indication	Regimen	TE?	AE #
Siblings	3063-202	M	10OCT2013	10OCT2013	VACCINE AGAINST DIPHTHERIA	ANTIINFECTIVES FOR SYSTEMIC USE	DIPHTHERIA VACCINE	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A
			10OCT2013	10OCT2013	VACCINE AGAINST HEPATITS B	ANTIINFECTIVES FOR SYSTEMIC USE	HEPATITIS B VACCINE	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A
			10OCT2013	10OCT2013	VACCINE AGAINST WHOOPING COUGH	ANTIINFECTIVES FOR SYSTEMIC USE	PERTUSSIS VACCINE	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A
			10OCT2013	10OCT2013	VACCINE AGAINST PNEUMOCOCCI	ANTIINFECTIVES FOR SYSTEMIC USE	PNEUMOCOCCAL VACCINE	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A
			10OCT2013	10OCT2013	VACCINE AGAINST POLIOMYELITIS	ANTIINFECTIVES FOR SYSTEMIC USE	POLIO VACCINE	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A
			10OCT2013	10OCT2013	VACCINE AGAINST TETANUS	ANTIINFECTIVES FOR SYSTEMIC USE	TETANUS VACCINE	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A
			11APR2014	11APR2013	VACCINE AGAINST DIPHTHERIA	ANTIINFECTIVES FOR SYSTEMIC USE	DIPHTHERIA VACCINE	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A
			11APR2014	11APR2014	VACCINE AGAINST HEPATITS B	ANTIINFECTIVES FOR SYSTEMIC USE	HEPATITIS B VACCINE	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A
			11APR2014	11APR2014	VACCINE AGAINST WHOOPING COUGH	ANTIINFECTIVES FOR SYSTEMIC USE	PERTUSSIS VACCINE	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A
			11APR2014	11APR2014	VACCINE AGAINST PNEUMOCOCCI	ANTIINFECTIVES FOR SYSTEMIC USE	PNEUMOCOCCAL VACCINE	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A
			11APR2014	11APR2014	VACCINE AGAINST POLIOMYELITIS	ANTIINFECTIVES FOR SYSTEMIC USE	POLIO VACCINE	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A
			11APR2014	11APR2014	VACCINE AGAINST TETANUS	ANTIINFECTIVES FOR SYSTEMIC USE	TETANUS VACCINE	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A

N/A = Not Applicable, Cont. = Continuing at end of study, TE (Treatment Emergent) = YES if the medication was started on Study Day 0 or later
* Treatment for the RSV infection in patient 3063-001 occurred at an outside hospital; not at the study research site.

Listing 16.2.4.3 Concomitant Medications

Cohort	Patient ID	Gender	Start Date(Day)	Stop Date(Day)	Medication	ATC1 Name	Preferred Term	Dose	Unit	Route	Indication	Regimen	TE?	AE #
Siblings	3063-202	M	21JUL2014	21JUL2014	VACCINE AGAINST MEASLES	ANTIINFECTIVES FOR SYSTEMIC USE	MEASLES VACCINE	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A
			21JUL2014	21JUL2014	VACCINE AGAINST MENINGOCOCCI	ANTIINFECTIVES FOR SYSTEMIC USE	MENINGOCOCCAL VACCINE	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A
			21JUL2014	21JUL2014	VACCINE AGAINST MUMPS	ANTIINFECTIVES FOR SYSTEMIC USE	MUMPS VACCINE	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A
			21JUL2014	21JUL2014	VACCINE AGAINST RUBELLA	ANTIINFECTIVES FOR SYSTEMIC USE	RUBELLA VACCINE	UNK	UNK	UNK	VACCINATION	1 DOSE	Yes	N/A
			05DEC2014	11DEC2014	AMOXICILLIN	ANTIINFECTIVES FOR SYSTEMIC USE	AMOXICILLIN	200	MG	ORL	RESPIRATORY INFECTION	3 TIMES PER DAY	Yes	AE
	3064-201	M	03MAY2011	Cont.	SALBUTAMOL INHALER	RESPIRATORY SYSTEM	SALBUTAMOL	4 TO 6 PUFFS	MICROGRAMS	ORAL	ASTHMA	PRN	Yes	N/A

N/A = Not Applicable, Cont. = Continuing at end of study, TE (Treatment Emergent) = YES if the medication was started on Study Day 0 or later
* Treatment for the RSV infection in patient 3063-001 occurred at an outside hospital; not at the study research site.

Listing 16.2.5 Study Drug Administration

Cohort	Patient ID	Gender	Day	Infusion Date (Day)	Infusion Start Time	Infusion Stop Time	Dose #	Total Dose (mg)	Complete Dose Given?	If no, Partial Dose (mg)
Cohort 1	3063-001	M	Day 0	18SEP2013(0)	12:05	12:40	1	11.40	Yes	
			Day 4	22SEP2013(4)	14:02	14:37	2	11.40	Yes	
			Day 7	25SEP2013(7)	12:00	12:35	3	11.40	Yes	
			Day 11	29SEP2013(11)	12:55	13:30	4	11.40	Yes	
			Day 14	02OCT2013(14)	12:55	13:30	5	11.40	Yes	
Cohort 1	1012-001	M	Day 0	02DEC2013(0)	11:12	11:42	1	11.40	Yes	
			Day 4	06DEC2013(4)	10:15	10:45	2	11.40	Yes	
			Day 7	09DEC2013(7)	09:45	10:15	3	11.40	Yes	
			Day 11	13DEC2013(11)	11:09	11:39	4	13.80	Yes	
			Day 14	16DEC2013(14)	10:00	10:30	5	13.80	Yes	
Cohort 1	1068-001	M	Day 0	05MAR2014(0)	09:15	09:59	1	10.80	Yes	
			Day 4	09MAR2014(4)	11:02	11:47	2	10.80	Yes	
			Day 7	12MAR2014(7)	09:17	10:02	3	10.80	Yes	
			Day 11	16MAR2014(11)	10:00	10:45	4	11.90	Yes	
			Day 14	19MAR2014(14)	11:16	12:01	5	11.90	Yes	
Cohort 2	3064-001	M	Day 0	09MAY2014(0)	14:00	16:00	1	31.55	Yes	
			Day 4	13MAY2014(4)	12:30	14:30	2	31.55	Yes	
			Day 7	16MAY2014(7)	12:00	14:00	3	31.55	Yes	
			Day 11	20MAY2014(11)	14:20	16:20	4	35.60	Yes	
			Day 14	23MAY2014(14)	11:30	13:30	5	37.20	Yes	
Cohort 2	3005-001	M	Day 0	04AUG2014(0)	10:00	12:00	1	35.00	Yes	
			Day 4	08AUG2014(4)	10:55	13:00	2	39.00	Yes	
			Day 7	11AUG2014(7)	10:20	12:15	3	39.30	Yes	
			Day 11	14AUG2014(10)	11:40	13:40	4	40.60	Yes	
			Day 14	18AUG2014(14)	12:28	14:28	5	47.10	Yes	
Cohort 2	3063-002	F	Day 0	02NOV2014(0)	12:27	13:00	1	30.00	Yes	
			Day 4	05NOV2014(3)	11:51	12:21	2	33.00	Yes	
			Day 7	09NOV2014(7)	12:45	13:15	3	33.00	Yes	
			Day 11	14NOV2014(12)	11:00	11:30	4	33.00	Yes	
			Day 14	16NOV2014(14)	12:45	13:15	5	33.00	Yes	

Listing 16.2.5 Study Drug Administration

Cohort	Patient ID	Gender	Day	Infusion Date (Day)	Infusion Start Time	Infusion Stop Time	Dose #	Total Dose (mg)	Complete Dose Given?	If no, Partial Dose (mg)
Cohort 2	3063-003	M	Day 0	26NOV2014(0)	12:55	13:25	1	28.00	Yes	
			Day 4	01DEC2014(5)	10:30	11:00	2	28.00	Yes	
			Day 7	04DEC2014(8)	11:50	12:20	3	32.00	Yes	
			Day 11	07DEC2014(11)	12:20	12:50	4	32.00	Yes	
			Day 14	10DEC2014(14)	11:45	12:15	5	32.00	Yes	
Cohort 2	3063-004	M	Day 0	05JAN2015(0)	14:16	14:46	1	26.00	Yes	
			Day 4	08JAN2015(3)	13:00	13:51	2	26.00	Yes	
			Day 7	12JAN2015(7)	11:50	12:20	3	26.00	Yes	
			Day 11	15JAN2015(10)	11:45	12:15	4	29.00	Yes	
			Day 14	19JAN2015(14)	12:00	12:30	5	29.00	Yes	
Cohort 3	1068-002	M	Day 0	27FEB2015(0)	07:15	08:15	1	76.00	Yes	
			Day 4	03MAR2015(4)	13:10	14:10	2	84.00	Yes	
			Day 7	06MAR2015(7)	10:38	13:35	3	84.00	Yes	
			Day 11	10MAR2015(11)	12:58	13:58	4	84.00	Yes	
			Day 14	13MAR2015(14)	11:05	12:04	5	84.00	Yes	
Cohort 3	3064-002	M	Day 0	09APR2015(0)	12:30	14:30	1	63.50	Yes	
			Day 4	13APR2015(4)	11:10	13:10	2	63.50	Yes	
			Day 7	16APR2015(7)	13:00	15:00	3	63.50	Yes	
			Day 11	20APR2015(11)	13:05	16:43	4	71.00	Yes	
			Day 14	23APR2015(14)	12:27	14:27	5	71.00	Yes	

Listing 16.2.6.1 Medical Questionnaire

Part 1 of 2

Cohort	Patient ID	Date (Day)	Full Term or Premature	# Weeks Premature	Reason Premature	Type of Birth	Reason for C-Section	Birth Weight (kg)	Birth Length (cm)	Birth Head Circumference (cm)
Cohort 1	3063-001	17SEP2013(-1)	Full-term			Vaginal		3.8	51.0	35.0
Cohort 1	1012-001	26NOV2013(-6)	Full-term			Vaginal		3.8	51.4	34.5
Cohort 1	1068-001	02MAR2014(-3)	Full-term			C-Section	PREVIOUS C-SECTION	3.8	52.1	35.5
Cohort 2	3064-001	08MAY2014(-1)	Full-term			Vaginal		3.3	51.5	34.4
Cohort 2	3005-001	31JUL2014(-4)	Full-term			C-Section		3.0	48.0	35.5
Cohort 2	3063-002	29OCT2014(-4)	Full-term			Vaginal		3.1	48.0	34.0
Cohort 2	3063-003	24NOV2014(-2)	Full-term			C-Section	FETAL GROWTH RESTRICTION	2.9	49.0	33.0
Cohort 2	3063-004	02JAN2015(-3)	Full-term			Vaginal		2.7	47.0	33.5
Cohort 3	1068-002	25FEB2015(-2)	Full-term			Vaginal		4.0	52.1	36.0
Cohort 3	3064-002	06APR2015(-3)	Full-term			Vaginal		3.2	ND	33.7

Listing 16.2.6.1 Medical Questionnaire

Part 2 of 2

Cohort	Patient ID	Date (Day)	Problems or Required NICU?	If Yes, Explain	Pass Newborn Screen?	Parts Not Passed	Days Old at Discharge	Any Other Problems in First Few Days of Life?	If Yes, Explain
Cohort 1	3063-001	17SEP2013(-1)	Yes	INCREASING BODY TEMP. TO 37.6 °C DURING EXAMINATION UNDER HEAT LAMP	Yes		*	No	
Cohort 1	1012-001	26NOV2013(-6)	No		Yes		1	No	
Cohort 1	1068-001	02MAR2014(-3)	Yes	CHEST X-RAY DUE TO ABNORMAL BREATHING/GRUNTING	Yes		4	No	
Cohort 2	3064-001	08MAY2014(-1)	Yes	JAUNDICE REQUIRING PHOTOTHERAPY	Yes		5	No	
Cohort 2	3005-001	31JUL2014(-4)	No		Yes		5	No	
Cohort 2	3063-002	29OCT2014(-4)	No		Yes		3	Yes	VERY DRY, SCALY SKIN
Cohort 2	3063-003	24NOV2014(-2)	No		Yes		4	No	
Cohort 2	3063-004	02JAN2015(-3)	No		Yes			No	
Cohort 3	1068-002	25FEB2015(-2)	No		Yes		4	Yes	JAUNDICE TREATED WITH BILI LIGHTS FOR 12 HOURS (BILI LEVELS OF 11.4 AT 72 HRS AND 10.0 AT 76 HRS); TONGUE TIE CLIPPED ON DAY 2 BY ENT
Cohort 3	3064-002	06APR2015(-3)	No		Yes		0	Yes	MILD TALIPES WHICH MIGHT REQUIRE PHYSIO

*Days old at discharge is blank for 3063-001 because the subject was never discharged. He was transferred from one hospital to another.

Listing 16.2.6.2 Growth and Development: Developmental Status

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Developmental Status for Gestational Age	If Abnormal, Explain
Cohort 1	1012-001	M	Baseline	26NOV2013(-6)	Normal	
	1068-001	M	Baseline	03MAR2014(-2)	Normal	
	3063-001	M	Baseline	17SEP2013(-1)	Normal	
Cohort 2	3005-001	M	Baseline	31JUL2014(-4)	Normal	
	3063-002	F	Baseline	29OCT2014(-4)	Normal	
	3063-003	M	Baseline	24NOV2014(-2)	Normal	
	3063-004	M	Baseline	04JAN2015(-1)	Normal	
	3064-001	M	Baseline	07MAY2014(-2)	Normal	
Cohort 3	1068-002	M	Baseline	25FEB2015(-2)	Normal	
	3064-002	M	Baseline	06APR2015(-3)	Normal	

Listing 16.2.6.3 Growth and Development: Feeding

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Feeding	If Abnormal, Explain
Cohort 1	1012-001	M	Baseline	26NOV2013(-6)	Normal	
	1068-001	M	Baseline	03MAR2014(-2)	Normal	
	3063-001	M	Baseline	17SEP2013(-1)	Normal	
Cohort 2	3005-001	M	Baseline	31JUL2014(-4)	Normal	
	3063-002	F	Baseline	29OCT2014(-4)	Normal	
	3063-003	M	Baseline	24NOV2014(-2)	Normal	
	3063-004	M	Baseline	04JAN2015(-1)	Normal	
	3064-001	M	Baseline	07MAY2014(-2)	Normal	
Cohort 3	1068-002	M	Baseline	25FEB2015(-2)	Normal	
	3064-002	M	Baseline	06APR2015(-3)	Normal	

Listing 16.2.6.4 Growth and Development: Bayley Scales II & III

Part 1 of 2

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Date of Birth	Chronological Age		Adjustment for Prematurity		Corrected Age		Mental Scale		Motor Scale	
						Months	Days	Months	Days	Months	Days	Raw Score	Mental Development Index	Raw Score	Psychomotor Development Index
Cohort 1	1012-001	M	Month 2	22JAN2014(51)	19NOV2013	2	3	0	0	2	3				
			Month 4	20MAR2014(108)	19NOV2013	4	1	0	0	4	1				
			Month 6	30MAY2014(179)	19NOV2013	6	8	0	0	0	0				
	1068-001	M	Month 2	22APR2014(48)	20FEB2014	2	2	0	0	2	2				
			Month 4	24JUN2014(111)	20FEB2014	4	4	0	0	4	4				
			Month 6	26AUG2014(174)	20FEB2014	6	6	0	0	6	6				
	3063-001	M	Month 2	20NOV2013(63)	15SEP2013	2	5	0	9	1	26	10	64	13	90
			Month 4	16JAN2014(120)	15SEP2013	4	1	0	9	3	22	37	85	25	89
			Month 6	24MAR2014(187)	15SEP2013	6	9	0	9	6	0	55	84	38	94
Cohort 2	3005-001	M	Month 2	08SEP2014(35)	08JUL2014	2	0	2	0	2	0				
			Month 4	10NOV2014(98)	08JUL2014	4	2	4	2	4	2				
			Month 6	12JAN2015(161)	08JUL2015	6	5	6	5	6	5				
	3063-002	F	Month 2	18DEC2014(46)	21OCT2014	1	27	0	0	1	27	26	96	18	105
			Month 4	23FEB2015(113)	21OCT2014	4	2	0	0	4	2	41	93	27	95
			Month 6	21APR2015(170)	21OCT2014	6	0	0	0	6	0	57	88	36	88
	3063-003	M	Month 2	15JAN2015(50)	17NOV2014	1	28	0	9	1	19	21	86	18	105
			Month 4	17MAR2015(111)	17NOV2014	4	0	0	9	3	21	41	93	24	86
			Month 6	19MAY2015(174)	17NOV2014	6	2	0	9	5	23	61	96	35	85
	3063-004	M	Month 2	27FEB2015(53)	31DEC2014	1	27	0	19	1	8	9	90	8	88
			Month 4	30APR2015(115)	31DEC2014	4	0	0	19	3	11	35	103	21	88
			Month 6	29JUN2015(175)	31DEC2014	5	28	0	19	5	9	57	103	32	94
	3064-001	M	Month 2	30JUN2014(52)	29APR2014	2	1	0	0	2	1				
			Month 4	01SEP2014(115)	29APR2014	4	2	0	0	4	2				
			Month 6	03NOV2014(178)	29APR2014	6	5	0	0	6	5				
Cohort 3	1068-002	M	Month 2	17APR2015(49)	15FEB2015	2	2	0	0	2	2				
			Month 4	19JUN2015(112)	15FEB2015	4	4	0	0	4	4				

Listing 16.2.6.4 Growth and Development: Bayley Scales II & III
Part 1 of 2

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Date of Birth	Chronological Age		Adjustment for Prematurity		Corrected Age		Mental Scale		Motor Scale	
						Months	Days	Months	Days	Months	Days	Raw Score	Mental Development Index	Raw Score	Psychomotor Development Index
Cohort 3	1068-002	M	Month 6	12AUG2015(166)	15FEB2015	5	28	0	0	5	28				
	3064-002	M	Month 2	01JUN2015(53)	30MAR2015	2	1	0	0	2	1				
			Month 4	03AUG2015(116)	30MAR2015	4	3	0	0	4	3				
			Month 6	28SEP2015(172)	30MAR2015	5	28	0	0	5	28				

Listing 16.2.6.4 Growth and Development: Bayley Scales II & III

Part 2 of 2

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Motor Composite Score: Sum of Scaled Scores	Motor Composite Score: Composite Score	Cognitive Comprehensive Score: Sum of Scaled Scores	Cognitive Comprehensive Score: Composite Score
Cohort 1	1012-001	M	Month 2	22JAN2014(51)	18	94	7	85
			Month 4	20MAR2014(108)	22	107	12	110
			Month 6	30MAY2014(179)	27	121	11	105
	1068-001	M	Month 2	22APR2014(48)				
			Month 4	24JUN2014(111)				
			Month 6	26AUG2014(174)				
	3063-001	M	Month 2	20NOV2013(63)				
			Month 4	16JAN2014(120)				
			Month 6	24MAR2014(187)				
Cohort 2	3005-001	M	Month 2	08SEP2014(35)				
			Month 4	10NOV2014(98)				
			Month 6	12JAN2015(161)				
	3063-002	F	Month 2	18DEC2014(46)				
			Month 4	23FEB2015(113)				
			Month 6	21APR2015(170)				
	3063-003	M	Month 2	15JAN2015(50)				
			Month 4	17MAR2015(111)				
			Month 6	19MAY2015(174)				
	3063-004	M	Month 2	27FEB2015(53)				
			Month 4	30APR2015(115)				
			Month 6	29JUN2015(175)				
	3064-001	M	Month 2	30JUN2014(52)	17	91	12	110
			Month 4	01SEP2014(115)	19	97	11	105
			Month 6	03NOV2014(178)	20	100	10	100
Cohort 3	1068-002	M	Month 2	17APR2015(49)				
			Month 4	19JUN2015(112)				
			Month 6	12AUG2015(166)				

Listing 16.2.6.4 Growth and Development: Bayley Scales II & III
Part 2 of 2

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Motor Composite Score		Cognitive Comprehensive Score	
					Sum of Scaled Scores	Composite Score	Sum of Scaled Scores	Composite Score
Cohort 3	3064-002	M	Month 2	01JUN2015(53)	22	107	11	105
			Month 4	03AUG2015(116)	27	121	13	115
			Month 6	28SEP2015(172)	15	85	10	100

Listing 16.2.6.5 Growth and Development: Denver Developmental Screening Test II

					Component				
Cohort	Patient ID	Gender	Visit	Study Date (Day)	Personal-Social	Fine Motor	Gross Motor	Other Growth Development Assessment?	If Yes, Please Specify
Cohort 1	1012-001	M	Month 2	22JAN2014(51)				No	
			Month 4	20MAR2014(108)				No	
			Month 6	30MAY2014(179)				No	
	1068-001	M	Month 2	22APR2014(48)	Normal For Age	Normal For Age	Normal For Age	No	
			Month 4	24JUN2014(111)	Normal For Age	Normal For Age	Normal For Age	No	
			Month 6	26AUG2014(174)	Normal For Age	Normal For Age	Normal For Age	No	
	3063-001	M	Month 2	20NOV2013(63)				No	
			Month 4	16JAN2014(120)				No	
			Month 6	24MAR2014(187)				No	
Cohort 2	3005-001	M	Month 2	08SEP2014(35)				No	
			Month 4	10NOV2014(98)				No	
			Month 6	12JAN2015(161)				No	
	3063-002	F	Month 2	18DEC2014(46)				No	
			Month 4	23FEB2015(113)				No	
			Month 6	21APR2015(170)				No	
	3063-003	M	Month 2	15JAN2015(50)				No	
			Month 4	17MAR2015(111)				No	
			Month 6	19MAY2015(174)				No	
	3063-004	M	Month 2	27FEB2015(53)				No	
			Month 4	30APR2015(115)				No	
			Month 6	29JUN2015(175)				No	
	3064-001	M	Month 2	30JUN2014(52)				No	
			Month 4	01SEP2014(115)				No	
			Month 6	03NOV2014(178)				No	

Listing 16.2.6.5 Growth and Development: Denver Developmental Screening Test II

					Component				
Cohort	Patient ID	Gender	Visit	Study Date (Day)	Personal-Social	Fine Motor	Gross Motor	Other Growth Development Assessment?	If Yes, Please Specify
Cohort 3	1068-002	M	Month 2	17APR2015(49)	Normal For Age	Normal For Age	Normal For Age	Yes	Feeding History Was Abnormal. Subject Had To Switch Formulas And Bottle Nipples And Was Currently Taking Increased Calories Per Ounce Of Formula
			Month 4	19JUN2015(112)	Normal For Age	Normal For Age	Normal For Age	No	
			Month 6	12AUG2015(166)	Normal For Age	Normal For Age	Normal For Age	No	
	3064-002	M	Month 2	01JUN2015(53)					
			Month 4	03AUG2015(116)				No	
			Month 6	28SEP2015(172)				No	

Listing 16.2.6.6 Dental Imaging

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Were Tooth Buds Present?	Number of Tooth Buds
Cohort 1	1012-001	M	Baseline	26NOV2013(-6)	Yes	4
	1068-001	M	Baseline	03MAR2014(-2)	No	
	3063-001	M	Baseline	17SEP2013(-1)	Yes	0
Cohort 2	3005-001	M	Baseline	31JUL2014(-4)	No	
	3063-002	F	Baseline	29OCT2014(-4)	Yes	9
	3063-003	M	Baseline	25NOV2014(-1)	Yes	2
	3063-004	M	Baseline	02JAN2015(-3)	Yes	2
	3064-001	M	Baseline	08MAY2014(-1)	Yes	4
Cohort 3	1068-002	M	Baseline	25FEB2015(-2)	Yes	4
	3064-002	M	Baseline	07APR2015(-2)	Yes	SOME HYPOPLASTIC TOOTH BUDS IN UPPER AND LOWER JAWS

Listing 16.2.6.7 Dental Exam

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Tooth Count		Tooth Shape	If Abnormal, Comments
					Baby Teeth	Adult Teeth		
Siblings	1068-201	M	Enrollment	22APR2014	20	0	Normal	
	3063-201	M	Enrollment	29OCT2014	0	0		
	3063-202	M	Enrollment	25NOV2014	2	0	Abnormal	CONICAL TEETH, POINTED
	3064-201	M	Enrollment	04NOV2014	1	0	Abnormal	CONICAL SHAPE, SLIGHTLY MORE POINTED THAN NORMAL LOWER LEFT CANINE

Listing 16.2.6.8 Facial Development

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Photograph View	If Lateral, Select Side
Cohort 1	1012-001	M	Baseline	26NOV2013(-6)	Both Frontal and Lateral	Both Right and Left
			Month 6	30MAY2014(179)	Both Frontal and Lateral	Both Right and Left
	1068-001	M	Baseline	03MAR2014(-2)	Both Frontal and Lateral	Both Right and Left
			Month 6	26AUG2014(174)	Both Frontal and Lateral	Both Right and Left
	3063-001	M	Baseline	17SEP2013(-1)	Both Frontal and Lateral	Both Right and Left
			Month 6	24MAR2014(187)	Both Frontal and Lateral	Both Right and Left
Cohort 2	3005-001	M	Baseline	01AUG2014(-3)	Both Frontal and Lateral	Both Right and Left
			Month 6	12JAN2015(161)	Both Frontal and Lateral	Both Right and Left
	3063-002	F	Baseline	29OCT2014(-4)	Both Frontal and Lateral	Both Right and Left
			Month 6	21APR2015(170)	Both Frontal and Lateral	Both Right and Left
	3063-003	M	Baseline	24NOV2014(-2)	Both Frontal and Lateral	Both Right and Left
			Month 6	18MAY2015(173)	Both Frontal and Lateral	Both Right and Left
	3063-004	M	Baseline	05JAN2015(0)	Both Frontal and Lateral	Both Right and Left
			Month 6	29JUN2015(175)	Both Frontal and Lateral	Both Right and Left
	3064-001	M	Baseline	07MAY2014(-2)	Both Frontal and Lateral	Both Right and Left
			Month 6	03NOV2014(178)	Both Frontal and Lateral	Both Right and Left
Cohort 3	1068-002	M	Baseline	26FEB2015(-1)	Both Frontal and Lateral	Right
			Month 6	12AUG2015(166)	Both Frontal and Lateral	Both Right and Left
	3064-002	M	Baseline	08APR2015(-1)	Both Frontal and Lateral	Both Right and Left
			Month 6	28SEP2015(172)	Both Frontal and Lateral	Both Right and Left
Siblings	1068-201	M	Enrollment	22APR2014	Both Frontal and Lateral	Both Right and Left
	3063-201	M	Enrollment	10NOV2014	Both Frontal and Lateral	Left
	3063-202	M	Enrollment	25NOV2014	Both Frontal and Lateral	Both Right and Left
	3064-201	M	Enrollment	03NOV2014	Both Frontal and Lateral	Both Right and Left

Listing 16.2.6.9 Pulmonary Function and eNO Levels

No Pulmonary or eNO Levels Data

Listing 16.2.6.10 Sweat Duct Density

No Sweat Duct Density Data

Listing 16.2.6.11 Stimulated Sweat Rate

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Start Time	End Time	Sweat Volume (uL)
Cohort 1	1012-001	M	Baseline	26NOV2013(-6)	14:56	15:26	0.0
			Month 2	22JAN2014(51)	10:40	11:10	0.0
			Month 6	30MAY2014(179)	13:01	13:31	2.5
	1068-001	M	Baseline	04MAR2014(-1)	13:30	14:00	0.0
			Month 2	22APR2014(48)	13:55	14:25	0.0
			Month 6	26AUG2014(174)	14:07	14:37	0.0
	3063-001	M	Baseline	17SEP2013(-1)	12:15	12:45	0.0
			Month 2	19NOV2013(62)	14:20	14:50	0.0
			Month 6	24MAR2014(187)	11:10	11:40	1.0
Cohort 2	3005-001	M	Baseline	31JUL2014(-4)	UNK	UNK	0.0
			Month 2	08SEP2014(35)	UNK	UNK	ND
			Month 6	12JAN2015(161)	12:15	12:35	0.0
	3063-002	F	Baseline	29OCT2014(-4)	13:30	14:00	2.0
			Month 2	18DEC2014(46)	11:50	12:20	47.0
			Month 6	21APR2015(170)	15:45	16:15	42.0
	3063-003	M	Baseline	24NOV2014(-2)	11:10	11:40	0.0
			Month 2	15JAN2015(50)	10:35	11:05	0.0
			Month 6	19MAY2015(174)	10:00	10:30	0.0
	3063-004	M	Baseline	02JAN2015(-3)	11:05	11:35	0.0
			Month 2	27FEB2015(53)	09:10	09:40	1.5
			Month 6	29JUN2015(175)	12:50	13:20	0.5
	3064-001	M	Baseline	09MAY2014(0)	10:30	11:30	0.3
			Month 2	30JUN2014(52)	10:00	10:30	0.0
			Month 6	03NOV2014(178)	10:20	10:50	0.0
Cohort 3	1068-002	M	Baseline	26FEB2015(-1)	12:37	13:07	0.0
			Month 2	17APR2015(49)	13:42	14:12	0.0
			Month 6	13AUG2015(167)	11:52	12:22	0.0
	3064-002	M	Baseline	07APR2015(-2)	10:30	11:00	NIL

Listing 16.2.6.11 Stimulated Sweat Rate

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Start Time	End Time	Sweat Volume (uL)
Cohort 3	3064-002	M	Month 2	01JUN2015(53)	10:45	11:30	0.0
			Month 6	28SEP2015(172)	11:40	12:10	0.0
Siblings	1068-201	M	Enrollment	22APR2014	14:09	14:41	46.0
	3063-201	M	Enrollment	29OCT2014	14:30	15:00	0.0
	3063-202	M	Enrollment	25NOV2014	11:30	12:00	0.0
	3064-201	M	Enrollment	30JUN2014	10:30	11:00	0.0

Listing 16.2.6.12 Dry Eye Assessment

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Corneal Exam		Eyelid Exam For Melbomian Gland Openings		NIBUT Assessed?	Right Eye (sec)	Left Eye (sec)
					Right Eye	Left Eye	Right Eye	Left Eye			
Cohort 1	1012-001	M	Baseline	26NOV2013(-6)	Normal	Normal	Present	Present	No		
			Month 2	22JAN2014(51)	Normal	Normal	Present	Present	No		
			Month 6	30MAY2014(179)	No Abnormalities Detected	No Abnormalities Detected	Present	Present	No		
	1068-001	M	Baseline	03MAR2014(-2)	Normal	Normal	Present	Present	No		
			Month 2	23APR2014(49)	No Abnormalities Detected	No Abnormalities Detected	Present	Present	No		
			Month 6	27AUG2014(175)	Abnormal	Abnormal	Present	Present	No		
	3063-001	M	Baseline	16SEP2013(-2)	Normal	Normal	Absent	Absent			
			Month 2	19NOV2013(62)	Normal	Normal	Absent	Absent			
			Month 6	24MAR2014(187)	Normal	Normal	Absent	Absent			
Cohort 2	3005-001	M	Baseline	30JUL2014(-5)	Normal	Normal	Absent	Absent	No		
			Month 2	08SEP2014(35)	Normal	Normal	Absent	Absent	No		
			Month 6	12JAN2015(161)	Normal	Normal	Absent	Present	No		
	3063-002	F	Baseline	29OCT2014(-4)	Normal	Normal	Present	Absent			
			Month 2	18DEC2014(46)	Normal	Normal	Present	Present	UA		
			Month 6	21APR2015(170)	Normal	Normal	Present	Present			
	3063-003	M	Baseline	25NOV2014(-1)	Normal	Normal	Absent	Absent			
			Month 2	15JAN2015(50)	Normal	Normal	Absent	Absent	No		
			Month 6	18MAY2015(173)	Normal	Normal	Present	Present	UA		
	3063-004	M	Baseline	05JAN2015(0)	Normal	Normal	Present	Present	No		
			Month 2	27FEB2015(53)	Normal	Normal	Present	Present	No		
			Month 6	29JUN2015(175)	Normal	Normal	Absent	Absent	UA		
	3064-001	M	Baseline	07MAY2014(-2)	Normal	Normal	Present	Present			
			Month 2	30JUN2014(52)	Normal	Normal	Present	Present	UA		
			Month 6	03NOV2014(178)	Normal	Normal	Present	Present	UA		
Cohort 3	1068-002	M	Baseline	25FEB2015(-2)	Normal	Normal	Present	Present	No		

NIBUT=Non-Invasive Break Up Time; UA=Unable to Assess; ND=Not Done;

Listing 16.2.6.12 Dry Eye Assessment

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Corneal Exam		Eyelid Exam For Melbomian Gland Openings		NIBUT Assessed?	Right Eye (sec)	Left Eye (sec)
					Right Eye	Left Eye	Right Eye	Left Eye			
Cohort 3	1068-002	M	Month 6	13AUG2015(167)	Normal	Normal	Present	Present	Yes	4	5
	3064-002	M	Baseline	08APR2015(-1)	Normal	Normal	Present	Present	No	ND	ND
			Month 6	28SEP2015(172)	Normal	Normal	Present	Present	No		
Siblings	1068-201	M	Enrollment	23APR2014	Normal	Normal	Present	Present	No		
	3063-201	M	Enrollment	29OCT2014	No Abnormalities Detected	No Abnormalities Detected	Absent	Absent	UA		
	3063-202	M	Enrollment	25NOV2014	Normal	Normal	Absent	Present	Yes	5	6
	3064-201	M	Enrollment	03NOV2014	Abnormal	Normal	Present	Present			

NIBUT=Non-Invasive Break Up Time; UA=Unable to Assess; ND=Not Done;

Listing 16.2.6.13 Ocular Surface Disease Index

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Total Number Questions Answered [1]	Subtotal Answers 1-5	Subtotal Answers 6-9	Subtotal Answers 10-12	Sum of Scores	OSDI Score [2]
Siblings	3063-201	M	Enrollment	29OCT2014	8	1	ND	0		

ND=Not Done
[1] Do not include questions answered N/A
[2] OSDI Score = (Sum of Scores*25)/Total number of questions answered

Listing 16.2.6.14 Tear Production (Schirmer Test)

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Tear Production (mm) Right Eye	Tear Production (mm) Left Eye
Siblings	3063-201	M	Enrollment	29OCT2014	ND	ND

Listing 16.2.6.15 Genetic Testing for XLHED

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Name of Laboratory Performing Testing	Result of Genetic Testing	How Was Test Conducted?
Cohort 1	1012-001	M	Baseline	29NOV2013(-3)	HARVARD MEDICAL SCHOOL-PARTNERS HEALTHCARE LABORATORY FOR MOLECULAR MEDICINE	POSITIVE. DNA SEQUENCING IDENTIFIED THE ASN185_PRO196DEL VARIANT IN EXON 4 OF THE EDA GENE, WHICH WAS PREVIOUSLY DETECTED IN THIS INDIVIDUAL'S MOTHER	Postnatally
	1068-001	M	Baseline	24FEB2014(-9)	LABORATORY FOR MOLECULAR MEDICINE	HEMIZYGOUS C.502+1G>A, INTRON 2, EDA, PATHOGENIC	Postnatally
	3063-001	M	Baseline	08AUG2013(-41)	INSTITUTE OF HUMAN GENETICS FREIBURG	DUPLICATION OF EXON 4 (= EXON 3 IN COMMON NOMENCLATURE)	Antenatally
Cohort 2	3005-001	M	Baseline	24JUL2014(-11)	SERVICE DE GENETIQUEMEDICALE-LE MANS	PRESENCE OF HEMIZYGOT MUTATION C.739C>T(P.GLN247*)	Postnatally
	3063-002	F	Baseline	09MAY2014(-177)	PRANATAL-MEDIZIN MUNCHEN	EDA C.467_468DEL, P.R156QFSX2, HETEROZYGOUS	Antenatally
	3063-003	M	Baseline	20NOV2014(-6)	AZIENDA OSPEDALIERO-UNIVERSIATRIA "A. MEYER"	EDA C.925-3C>G, HEMIZYGOUS	Postnatally
	3063-004	M	Baseline	02JAN2015(-3)	PEDIATRIC RESEARCH CENTER ERLANGEN	EDA C.463C>T, P.R155C, HEMIZYGOUS	Postnatally
	3064-001	M	Baseline	02MAY2014(-7)	ALL WALES MOLECULAR GENETICS LABORATORY	HEMIZYGOUS FOR EDAC.467G>A	Postnatally
Cohort 3	1068-002	M	Baseline	15FEB2015(-12)	LABORATORY FOR MOLECULAR MEDICINE	HEMIZYGOUS C.467G>T (P.ARG156LEU), EXON 2, EDA, PATHOGENIC	Postnatally
	3064-002	M	Baseline	01APR2015(-8)	ALL WALES MOLECULAR GENETIC LABORATORY	EDA C.1049 G>T	Postnatally

Listing 16.2.6.16 Genetic Testing for Polymorphism EDAR V370A

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Name of Laboratory Performing Testing	Result of Genetic Testing
Cohort 1	1068-001	M	Baseline	24FEB2014(-9)	LABORATORY FOR MOLECULAR MEDICINE	ABSENT
	3063-001	M	Baseline	17SEP2013(-1)	DEP MOLECULAR PEDIATRICS ERLANGEN	NO POLYMORPHISM V370 A
Cohort 2	3063-002	F	Baseline	29OCT2014(-4)	PEDIATRIC RESEARCH CENTER, UNIVERSITY HOSPITAL ERLANGEN	NO POLYMORPHISM AT POSITION V370 IN EDAR
	3063-003	M	Baseline	25NOV2014(-1)	PEDIATRIC RESEARCH CENTER ERLANGEN	NO POLYMORPHISM EDAR V370A
	3063-004	M	Baseline	05JAN2015(0)	PEDIATRIC RESEARCH CENTER ERLANGEN	NO EDAR V370A
	3064-001	M	Baseline	06JUN2014(28)	ALL WALES MOLECULAR GENETIC LABORATORY	EDAR C. 1109T>C ABSENT
Cohort 3	1068-002	M	Baseline	18FEB2015(-9)	LABORATORY FOR MOLECULAR MEDICINE	V370A POLYMORPHISM - ABSENT
	3064-002	M	Baseline	30MAR2015(-10)	UNIVERSITY HOSPITAL OF WALES,	EDA C.1049G>T

Listing 16.2.7 Adverse Events

Cohort	Patient ID	AE #	Event	System Organ Class	Preferred Term	Date of Onset (Day)	Resolved or Death Date (Day)	SAE? Specify	---Grade--- CTCAE	IA	Relat	Study Med Action	Treat	Out	WD?	TEAE
Cohort 1	3063-001	14	PERSISTENT HIGH NEUTROPHILS	INVESTIGATIONS	NEUTROPHIL COUNT INCREASED	17SEP2013(-1)	19SEP2013(1)	No	MI	MI	NOT	NO	NO	R	No	No
		15	PERSISTENT LOW MONOCYTES	INVESTIGATIONS	MONOCYTE COUNT DECREASED	17SEP2013(-1)	19SEP2013(1)	No	MI	MI	NOT	NO	NO	R	No	No
		16	PERSISTENT HIGH HAEMATOCRIT	INVESTIGATIONS	HAEMATOCRIT INCREASED	17SEP2013(-1)	04OCT2013(16)	No	MI	MI	NOT	NO	NO	R	No	No
		17	PERSISTENT LOW PLATELETS	INVESTIGATIONS	PLATELET COUNT DECREASED	17SEP2013(-1)	04OCT2013(16)	No	MI	MI	NOT	NO	NO	R	No	No
		20	HIGH BLOOD EOSINOPHILS	INVESTIGATIONS	EOSINOPHIL COUNT INCREASED	19SEP2013(1)	04OCT2013(16)	No	MI	MI	POS	NO	NO	R	No	Yes
		22	LOW CREATININE	INVESTIGATIONS	BLOOD CREATININE DECREASED	20SEP2013(2)	19NOV2013(62)	No	MI	MI	POS	NO	NO	R	No	Yes
		1	HYPOALBUMINEMIA	METABOLISM AND NUTRITION DISORDERS	HYPOALBUMINAEMIA	04OCT2013(16)	22OCT2013(34)	No	MI	MI	POS	NO	NO	R	No	Yes
		18	HIGH HAEMOGLOBIN	INVESTIGATIONS	HAEMOGLOBIN INCREASED	04OCT2013(16)	09OCT2013(21)	No	MI	MI	POS	NO	NO	R	No	Yes
		19	HIGH GLUCOSE	INVESTIGATIONS	BLOOD GLUCOSE INCREASED	04OCT2013(16)	20NOV2013(63)	No	MI	MI	POS	NO	NO	R	No	Yes
		2	HYPONATREMIA	METABOLISM AND NUTRITION DISORDERS	HYPONATRAEMIA	04OCT2013(16)	11OCT2013(23)	No	SE	MI	POS	NO	NO	R	No	Yes
		21	LOW BUN	INVESTIGATIONS	BLOOD UREA DECREASED	04OCT2013(16)	09OCT2013(21)	No	MI	MI	POS	NO	NO	R	No	Yes
		3	SIGN OF LOCAL SKIN INFLAMMATION AT THE BIOPSY SITE	SKIN AND SUBCUTANEOUS TISSUE DISORDERS	DERMATITIS	11OCT2013(23)	13OCT2013(25)	No	MI	MI	NOT	NO	NO	R	No	Yes

SAE Specify: D=Death, LT=Life Threatening, HO=Hospitalization or prolonged hospitalization, DI=Persistent or significant disability/ incapacity,
CA=Congenital anomaly/birth defect, IM=Important medical event;
Grade: IA=Per Investigator Assessment, MI=Mild, MO=Moderate, SE=Severe, LT=Life Threatening, D=Death;
Relat=Relation to Study Medication: DEF=Definitely Related, PRO=Probably Related, POS=Possibly Related, UNL=Unlikely Related, NOT=Not Related;
Study Med Action=Action Taken with Study Medication: NO=None, INT=Study Medication Interrupted, DC=Study Medication Discontinued;
Treat=Treatment for Event: NO=None, MA=Medication Administered, NDT=Non-drug Therapy Administered, OM=Other Medication(s) Dose Modified;
Out=Outcome of Event: R=Resolved, RS=Resolved with Sequelae, UR=Unresolved, D=Death, U=Unknown;
WD=Did the AE cause Withdrawal; TEAE=Treatment Emergent AE

Listing 16.2.7 Adverse Events

Cohort	Patient ID	AE #	Event	System Organ Class	Preferred Term	Date of Onset (Day)	Resolved or Death Date (Day)	SAE? Specify	---Grade--- CTCAE	IA	Relat	Study Med Action	Treat	Out	WD?	TEAE
Cohort 1	3063-001	4	HYPOALBUMINAEMIA	METABOLISM AND NUTRITION DISORDERS	HYPOALBUMINAEMIA	20NOV2013(63)	16JAN2014(120)	No	MI	MI	POS	NO	NO	R	No	Yes
		5	RESPIRATORY SYNCYTIAL VIRUS INFECTION	INFECTIONS AND INFESTATIONS	RESPIRATORY SYNCYTIAL VIRUS INFECTION	11FEB2014(146)	14FEB2014(149)	Yes -HO	SE	SE	NOT	NO	MA	R	No	Yes
		23	LOW BASOPHILS (PERSISTING)	INVESTIGATIONS	BASOPHIL COUNT DECREASED	24MAR2014(187)		No	MI	MI	POS	NO	NO	UR	No	Yes
		24	LOW MONOCYTES (PERSISTING)	INVESTIGATIONS	MONOCYTE COUNT DECREASED	24MAR2014(187)		No	MI	MI	POS	NO	NO	UR	No	Yes
		25	HIGH HEMATOCRIT (PERSISTING)	INVESTIGATIONS	HAEMATOCRIT INCREASED	24MAR2014(187)		No	MI	MI	POS	NO	NO	UR	No	Yes
		26	HIGH RBC (PERSISTING)	INVESTIGATIONS	RED BLOOD CELL COUNT INCREASED	24MAR2014(187)		No	MI	MI	POS	NO	NO	UR	No	Yes
		27	PERSISTING LOW CREATININE	INVESTIGATIONS	BLOOD CREATININE DECREASED	24MAR2014(187)		No	MI	MI	POS	NO	NO	UR	No	Yes
		6	EOSINOPHILIA	BLOOD AND LYMPHATIC SYSTEM DISORDERS	EOSINOPHILIA	24MAR2014(187)		No	MI	MI	NOT	NO	NO	UR	No	Yes
Cohort 1	1012-001	1	PCO2 HIGH	INVESTIGATIONS	PCO2 INCREASED	03DEC2013(1)		No	MI	MI	UNL	NO	NO	UR	No	Yes
		2	HIGH BICARBONATE ON CMP	INVESTIGATIONS	BLOOD BICARBONATE INCREASED	03DEC2013(1)		No	MI	MI	UNL	NO	NO	UR	No	Yes
		3	LOW O2 SATURATION	INVESTIGATIONS	OXYGEN SATURATION DECREASED	03DEC2013(1)		No	MI	MI	UNL	NO	NO	UR	No	Yes
		4	LOW PO2	INVESTIGATIONS	PO2 DECREASED	03DEC2013(1)		No	MI	MI	UNL	NO	NO	UR	No	Yes
		5	BENIGN NEVUS FLAMMEUS ON OCCIPUT	CONGENITAL, FAMILIAL AND GENETIC DISORDERS	NAEVUS FLAMMEUS	05DEC2013(3)		No	MI	MI	UNL	NO	NO	UR	No	Yes

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Listing 16.2.7 Adverse Events

Cohort	Patient ID	AE #	Event	System Organ Class	Preferred Term	Date of Onset (Day)	Resolved or Death Date (Day)	SAE? Specify	---Grade--- CTCAE	IA	Relat	Study Med Action	Treat	Out	WD?	TEAE
Cohort 1	1012-001	6	LOW HEMOGLOBIN	INVESTIGATIONS	HAEMOGLOBIN DECREASED	18DEC2013(16)	23DEC2013(21)	No	MI	MI	UNL	NO	NO	R	No	Yes
		7	LOW HEMATOCRIT	INVESTIGATIONS	HAEMATOCRIT DECREASED	18DEC2013(16)	23DEC2013(21)	No	MI	MI	UNL	NO	NO	R	No	Yes
		8	INTERMITTENT LOW SERUM CREATININE	INVESTIGATIONS	BLOOD CREATININE DECREASED	18DEC2013(16)		No	MI	MI	UNL	NO	NO	UR	No	Yes
		9	TRACE WBC ESTERASE IN URINALYSIS	INVESTIGATIONS	URINE LEUKOCYTE ESTERASE POSITIVE	23DEC2013(21)	22JAN2014(51)	No	MI	MI	UNL	NO	NO	R	No	Yes
		10	INTERMITTENT UPPER RESPIRATORY INFECTION	INFECTIONS AND INFESTATIONS	UPPER RESPIRATORY TRACT INFECTION	22JAN2014(51)		No	MI	MI	UNL	NO	NO	UR	No	Yes
		11	LOW UREA NITROGEN IN SERUM	INVESTIGATIONS	BLOOD UREA DECREASED	22JAN2014(51)	30MAY2014(179)	No	MI	MI	UNL	NO	NO	R	No	Yes
		17	DECREASED HEMATOCRIT	INVESTIGATIONS	HAEMATOCRIT DECREASED	22JAN2014(51)	30MAY2014(179)	No	MI	MI	UNL	NO	NO	R	No	Yes
		13	LOW MCH	INVESTIGATIONS	MEAN CELL HAEMOGLOBIN DECREASED	30MAY2014(179)		No	MI	MI	NOT	NO	NO	UR	No	Yes
		14	HIGH MONOCYTES	INVESTIGATIONS	MONOCYTE COUNT INCREASED	30MAY2014(179)		No	MI	MI	UNL	NO	NO	UR	No	Yes
		15	HIGH RBC	INVESTIGATIONS	RED BLOOD CELL COUNT INCREASED	30MAY2014(179)		No	MI	MI	NOT	NO	NO	UR	No	Yes
		16	LOW NEUTROPHILS	INVESTIGATIONS	NEUTROPHIL COUNT DECREASED	30MAY2014(179)		No	MO	MI	NOT	NO	NO	UR	No	Yes
Cohort 1	1068-001	12	ABNORMAL TRACE POIKILOCYTOSIS ON CBC	BLOOD AND LYMPHATIC SYSTEM DISORDERS	POIKILOCYTOSIS	06MAR2014(1)	21MAR2014(16)	No	MI	MI	UNL	NO	NO	R	No	Yes

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Grade: IA=Per Investigator Assessment, MI=Mild, MO=Moderate, SE=Severe, LT=Life Threatening, D=Death;
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Cohort 1	1068-001	13	ABNORMAL MACROCYTES ON CBC	BLOOD AND LYMPHATIC SYSTEM DISORDERS	MACROCYTOSIS	06MAR2014(1)	21MAR2014(16)	No	MI	MI	UNL	NO	NO	R	No	Yes
		14	ABNORMAL TEAR DROP CELLS ON CBC	BLOOD AND LYMPHATIC SYSTEM DISORDERS	RED BLOOD CELL ABNORMALITY	06MAR2014(1)	21MAR2014(16)	No	MI	MI	UNL	NO	NO	R	No	Yes
		7	HIGH MCH ON CBC	INVESTIGATIONS	MEAN CELL HAEMOGLOBIN INCREASED	06MAR2014(1)	21MAR2014(16)	No	MI	MI	UNL	NO	NO	R	No	Yes
		9	HIGH PLATELETS ON CBC	INVESTIGATIONS	PLATELET COUNT INCREASED	06MAR2014(1)	21MAR2014(16)	No	MI	MI	UNL	NO	NO	R	No	Yes
		18	HIGH POTASSIUM ON CMP	INVESTIGATIONS	BLOOD POTASSIUM INCREASED	21MAR2014(16)	26AUG2014(174)	No	MI	MI	UNL	NO	NO	R	No	Yes
		22	CLOUDY URINALYSIS	RENAL AND URINARY DISORDERS	URINE ABNORMALITY	21MAR2014(16)	26MAR2014(21)	No	MI	MI	UNL	NO	NO	R	No	Yes
		24	LOW NEUTROPHILS ON CBC	INVESTIGATIONS	NEUTROPHIL COUNT DECREASED	26MAR2014(21)	22APR2014(48)	No	MI	MI	UNL	NO	NO	R	No	Yes
		26	YOUNG LYMPHOCYTES ON CBC	INVESTIGATIONS	LYMPHOCYTE MORPHOLOGY ABNORMAL	26MAR2014(21)	22APR2014(48)	No	MI	MI	UNL	NO	NO	R	No	Yes
		29	HIGH ALT ON CMP	INVESTIGATIONS	ALANINE AMINOTRANSFERASE INCREASED	22APR2014(48)	26AUG2014(174)	No	MI	MI	UNL	NO	NO	R	No	Yes
		30	HIGH AST ON CMP	INVESTIGATIONS	ASPARTATE AMINOTRANSFERASE INCREASED	22APR2014(48)	26AUG2014(174)	No	MI	MI	UNL	NO	NO	R	No	Yes
		31	HIGH PLATELET COUNT	INVESTIGATIONS	PLATELET COUNT INCREASED	22APR2014(48)	26AUG2014(174)	No	MI	MI	UNL	NO	NO	R	No	Yes

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Grade: IA=Per Investigator Assessment, MI=Mild, MO=Moderate, SE=Severe, LT=Life Threatening, D=Death;
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Cohort 1	1068-001	32	POIKILOCYTOSIS ON CBC	BLOOD AND LYMPHATIC SYSTEM DISORDERS	POIKILOCYTOSIS	22APR2014(48)		No	MI	MI	UNL	NO	NO	UR	No	Yes
		34	MICROCYTES ON CBC	INVESTIGATIONS	RED BLOOD CELL MICROCYTES PRESENT	26AUG2014(174)		No	MI	MI	UNL	NO	NO	UR	No	Yes
		35	OVALOCYTES ON CBC	INVESTIGATIONS	RED BLOOD CELL ELLIPTOCYTES PRESENT	26AUG2014(174)		No	MI	MI	UNL	NO	NO	UR	No	Yes
		36	TEAR DROP CELLS ON CBC	BLOOD AND LYMPHATIC SYSTEM DISORDERS	RED BLOOD CELL ABNORMALITY	26AUG2014(174)		No	MI	MI	UNL	NO	NO	UR	No	Yes
		37	CLOUDY CLARITY ON URINALYSIS	RENAL AND URINARY DISORDERS	URINE ABNORMALITY	26AUG2014(174)		No	MI	MI	UNL	NO	NO	UR	No	Yes
Cohort 2	3064-001	1	INCREASED WHITE BLOOD CELL COUNT.	INVESTIGATIONS	WHITE BLOOD CELL COUNT INCREASED	10MAY2014(1)	16MAY2014(7)	No	MI	MI	UNL	NO	NO	R	No	Yes
		19	PERSISTENT LOW ALBUMIN	INVESTIGATIONS	BLOOD ALBUMIN DECREASED	10MAY2014(1)	12MAY2014(3)	No	MI	MI	UNL	NO	NO	R	No	Yes
		2	HIGH NEUTROPHIL COUNT	INVESTIGATIONS	NEUTROPHIL COUNT INCREASED	10MAY2014(1)	16MAY2014(7)	No	MI	MI	UNL	NO	NO	R	No	Yes
		20	PERSISTENT HIGH MONOCYTES	INVESTIGATIONS	MONOCYTE COUNT INCREASED	10MAY2014(1)	30MAY2014(21)	No	MI	MI	UNL	NO	NO	R	No	Yes
		6	HIGH LYMPHOCYTE COUNT	INVESTIGATIONS	LYMPHOCYTE COUNT INCREASED	10MAY2014(1)	12MAY2014(3)	No	MI	MI	NOT	NO	NO	R	No	Yes
		5	INCREASED BASOPHILS	INVESTIGATIONS	BASOPHIL COUNT INCREASED	12MAY2014(3)	30MAY2014(21)	No	MI	MI	NOT	NO	NO	R	No	Yes
		10	LOW CREATININE	INVESTIGATIONS	BLOOD CREATININE DECREASED	13MAY2014(4)	16MAY2014(7)	No	MI	MI	NOT	NO	NO	R	No	Yes

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Cohort 2	3064-001	3	INCREASED PLATELET COUNT	INVESTIGATIONS	PLATELET COUNT INCREASED	13MAY2014(4)		No	MI	MI	NOT	NO	NO	UR	No	Yes
		7	WORSENING OF LOW ALBUMEN LEVEL	INVESTIGATIONS	BLOOD ALBUMIN DECREASED	13MAY2014(4)	03NOV2014(178)	No	MI	MI	NOT	NO	NO	R	No	Yes
		8	HYPERCALCAEMIA	METABOLISM AND NUTRITION DISORDERS	HYPERCALCAEMIA	13MAY2014(4)	19MAY2014(10)	No	MI	MI	NOT	NO	NO	R	No	Yes
		18	INCREASED WHITE CELL COUNT	INVESTIGATIONS	WHITE BLOOD CELL COUNT INCREASED	19MAY2014(10)	25MAY2014(16)	No	MI	MI	UNL	NO	NO	R	No	Yes
		4	LOW HAEMOGLOBIN COUNT	INVESTIGATIONS	HAEMOGLOBIN DECREASED	25MAY2014(16)	03NOV2014(178)	No	MI	MI	NOT	NO	NO	R	No	Yes
		9	HYPERCALCAEMIA	METABOLISM AND NUTRITION DISORDERS	HYPERCALCAEMIA	30MAY2014(21)	30JUN2014(52)	No	MI	MI	NOT	NO	NO	R	No	Yes
		21	OUT OF RANGE RESULT - LOW HAEMATICRIT	INVESTIGATIONS	HAEMATOCRIT DECREASED	30JUN2014(52)	03NOV2014(178)	No	MI	MI	NOT	NO	NO	R	No	Yes
		16	IRRITABLE FOLLOWING IMMUNISATION	PSYCHIATRIC DISORDERS	IRRITABILITY	03JUL2014(55)	03JUL2014(55)	No	MI	MI	NOT	NO	MA	R	No	Yes
		12	SPARSE HAIR	SKIN AND SUBCUTANEOUS TISSUE DISORDERS	HAIR GROWTH ABNORMAL	01SEP2014(115)		No	MI	MI	NOT	NO	NO	UR	No	Yes
		13	THIN HAIR	SKIN AND SUBCUTANEOUS TISSUE DISORDERS	HAIR DISORDER	01SEP2014(115)		No	MI	MI	NOT	NO	NO	UR	No	Yes
		17	OTITIS MEDIA	INFECTIONS AND INFESTATIONS	OTITIS MEDIA	25OCT2014(169)	02NOV2014(177)	No	MO	MO	NOT	NO	MA	R	No	Yes

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Cohort 2	3064-001	11	HIGH CREATININE	INVESTIGATIONS	BLOOD CREATININE INCREASED	03NOV2014(178)		No	MI	MI	NOT	NO	NO	UR	No	Yes
		14	DRY PATCH OF SKIN TO LEFT SCALP AREA	SKIN AND SUBCUTANEOUS TISSUE DISORDERS	DRY SKIN	03NOV2014(178)		No	MI	MI	NOT	NO	NO	UR	No	Yes
		15	DRY SKIN TO SOLES OF FEET BILATERALLY	SKIN AND SUBCUTANEOUS TISSUE DISORDERS	DRY SKIN	03NOV2014(178)		No	MI	MI	NOT	NO	NO	UR	No	Yes
Cohort 2	3005-001	10	LOW HEMATOCRIT	INVESTIGATIONS	HAEMATOCRIT DECREASED	31JUL2014(-4)	08SEP2014(35)	No	MI	MI	NOT	NO	NO	R	No	No
		11	ELEVATED NEUTROPHILS	INVESTIGATIONS	NEUTROPHIL COUNT INCREASED	31JUL2014(-4)	08SEP2014(35)	No	MI	MI	NOT	NO	NO	R	No	No
		12	ELEVATED LYMPHOCYTES	INVESTIGATIONS	LYMPHOCYTE COUNT INCREASED	31JUL2014(-4)	08SEP2014(35)	No	MI	MI	NOT	NO	NO	R	No	No
		13	ELEVATED MONOCYTES	INVESTIGATIONS	MONOCYTE COUNT INCREASED	31JUL2014(-4)	08SEP2014(35)	No	MI	MI	NOT	NO	NO	R	No	No
		14	ELEVATED EOSINOPHILES	INVESTIGATIONS	EOSINOPHIL COUNT INCREASED	31JUL2014(-4)		No	MI	MI	NOT	NO	NO	UR	No	No
		6	LOW ALBUMINE	INVESTIGATIONS	BLOOD ALBUMIN DECREASED	31JUL2014(-4)	20AUG2014(16)	No	MI	MI	NOT	NO	NO	R	No	No
		8	LOW HEMOGLOBIN	INVESTIGATIONS	HAEMOGLOBIN DECREASED	31JUL2014(-4)	08SEP2014(35)	No	MI	MI	NOT	NO	NO	R	No	No
		9	LOW RBC	INVESTIGATIONS	RED BLOOD CELL COUNT DECREASED	31JUL2014(-4)		No	MI	MI	NOT	NO	NO	UR	No	No
		4	ELEVATED CHLORIDES	INVESTIGATIONS	BLOOD CHLORIDE INCREASED	05AUG2014(1)	25AUG2014(21)	No	MI	MI	NOT	NO	NO	R	No	Yes

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Cohort 2	3005-001	5	ELEVATED ALKALINE PHOSPHATASE	INVESTIGATIONS	BLOOD ALKALINE PHOSPHATASE INCREASED	05AUG2014(1)	12JAN2015(161)	No	MI	MI	NOT	NO	NO	R	No	Yes
		1	ANEMIA	BLOOD AND LYMPHATIC SYSTEM DISORDERS	ANAEMIA	06AUG2014(2)		No	MI	MI	NOT	NO	MA	UR	No	Yes
		7	HIGH GLUCOSE	INVESTIGATIONS	BLOOD GLUCOSE INCREASED	20AUG2014(16)	25AUG2014(21)	No	MI	MI	NOT	NO	NO	R	No	Yes
		5	PYELONEPHRITIS	INFECTIONS AND INFESTATIONS	PYELONEPHRITIS	21SEP2014(48)	24SEP2014(51)	Yes -HO	MO	MO	UNL	NO	MA	R	No	Yes
		2	PHARYNGITIS	INFECTIONS AND INFESTATIONS	PHARYNGITIS	09OCT2014(66)	12OCT2014(69)	No	MI	MI	NOT	NO	MA	R	No	Yes
		4	PHARYNGITIS	INFECTIONS AND INFESTATIONS	PHARYNGITIS	02DEC2014(120)	06DEC2014(124)	No	MI	MI	NOT	NO	MA	R	No	Yes
Cohort 2	3063-002	14	PERSISTENT LOW MONOCYTES	INVESTIGATIONS	MONOCYTE COUNT DECREASED	29OCT2014(-4)	03NOV2014(1)	No	MI	MI	NOT	NO	NO	R	No	No
		19	LOW ALBUMIN	INVESTIGATIONS	BLOOD ALBUMIN DECREASED	29OCT2014(-4)	23NOV2014(21)	No	MI	MI	POS	NO	NO	R	No	No
		7	PERSISTENT LOW RBC	INVESTIGATIONS	RED BLOOD CELL COUNT DECREASED	29OCT2014(-4)	03NOV2014(1)	No	MI	MI	NOT	NO	NO	R	No	No
		8	PERSISTENT HIGH GLUCOSE	INVESTIGATIONS	BLOOD GLUCOSE INCREASED	29OCT2014(-4)	23NOV2014(21)	No	MI	MI	NOT	NO	NO	R	No	No
		9	PERSISTENT HIGH CALCIUM	INVESTIGATIONS	BLOOD CALCIUM INCREASED	29OCT2014(-4)	03NOV2014(1)	No	MI	MI	NOT	NO	NO	R	No	No
		1	EOSINOPHILIA	BLOOD AND LYMPHATIC SYSTEM DISORDERS	EOSINOPHILIA	03NOV2014(1)	12NOV2014(10)	No	MI	MI	POS	NO	NO	R	No	Yes

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Cohort 2	3063-002	10	LOW CREATININE	INVESTIGATIONS	BLOOD CREATININE DECREASED	12NOV2014(10)	21APR2015(170)	No	MI	MI	POS	NO	NO	R	No	Yes
		11	HIGH CHLORIDE	INVESTIGATIONS	BLOOD CHLORIDE INCREASED	12NOV2014(10)	23NOV2014(21)	No	MI	MI	POS	NO	NO	R	No	Yes
		2	FEBRILE UPPER RESPIRATORY INFECTION	INFECTIONS AND INFESTATIONS	UPPER RESPIRATORY TRACT INFECTION	12NOV2014(10)	18NOV2014(16)	Yes -IM	SE	MO	UNL	NO	MA	R	No	Yes
		25	HIGH WBC	INVESTIGATIONS	WHITE BLOOD CELL COUNT INCREASED	12NOV2014(10)	14NOV2014(12)	No		MI	UNL	NO	NO	R	No	Yes
		26	HIGH PLATELETS	INVESTIGATIONS	PLATELET COUNT INCREASED	12NOV2014(10)	18NOV2014(16)	No	MI	MI	UNL	NO	NO	R	No	Yes
		27	HIGH NEUTROPHILS	INVESTIGATIONS	NEUTROPHIL COUNT INCREASED	12NOV2014(10)	14NOV2014(12)	No	MI	MI	UNL	NO	NO	R	No	Yes
		28	HIGH MONOCYTES	INVESTIGATIONS	MONOCYTE COUNT INCREASED	12NOV2014(10)	14NOV2014(12)	No	MI	MI	UNL	NO	NO	R	No	Yes
		29	HIGH BASOPHILS	INVESTIGATIONS	BASOPHIL COUNT INCREASED	12NOV2014(10)	23NOV2014(21)	No	MI	MI	UNL	NO	NO	R	No	Yes
		3	THROMBOCYTOSIS	BLOOD AND LYMPHATIC SYSTEM DISORDERS	THROMBOCYTOSIS	12NOV2014(10)	18NOV2014(16)	No	MI	MI	UNL	NO	NO	R	No	Yes
		12	HIGH MONOCYTES	INVESTIGATIONS	MONOCYTE COUNT INCREASED	18NOV2014(16)	23NOV2014(21)	No	MI	MI	POS	NO	NO	R	No	Yes
		13	HIGH BASOPHILS	INVESTIGATIONS	BASOPHIL COUNT INCREASED	18NOV2014(16)	23NOV2014(21)	No	MI	MI	POS	NO	NO	R	No	Yes
		15	HIGH HEMOGLOBIN	INVESTIGATIONS	HAEMOGLOBIN INCREASED	23NOV2014(21)	18DEC2014(46)	No	MI	MI	POS	NO	NO	R	No	Yes
		16	LOW NEUTROPHILS	INVESTIGATIONS	NEUTROPHIL COUNT DECREASED	18DEC2014(46)	21APR2015(170)	No	MI	MI	POS	NO	NO	R	No	Yes

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Cohort 2	3063-002	17	PERSISTING HIGH BASOPHILS	INVESTIGATIONS	BASOPHIL COUNT INCREASED	21APR2015(170)		No	MI	MI	POS	NO	NO	UR	No	Yes
		18	PERSISTING HIGH HEMATOCRIT	INVESTIGATIONS	HAEMATOCRIT INCREASED	21APR2015(170)		No	MI	MI	POS	NO	NO	UR	No	Yes
		20	HIGH WHITE CELL COUNT	INVESTIGATIONS	WHITE BLOOD CELL COUNT INCREASED	21APR2015(170)		No		MI	POS	NO	NO	UR	No	Yes
		4	HYPERCHLOREMIA	METABOLISM AND NUTRITION DISORDERS	HYPERCHLORAEMIA	21APR2015(170)		No	MI	MI	UNL	NO	NO	UR	No	Yes
		5	LYMPHOCYTOSIS	BLOOD AND LYMPHATIC SYSTEM DISORDERS	LYMPHOCYTOSIS	21APR2015(170)		No	MI	MI	UNL	NO	NO	UR	No	Yes
Cohort 2	3063-003	1	NEONATAL ANEMIA	BLOOD AND LYMPHATIC SYSTEM DISORDERS	ANAEMIA NEONATAL	24NOV2014(-2)		No	MI	MI	NOT	NO	NO	UR	No	No
		10	PERSISTENT HIGH CHLORIDE	INVESTIGATIONS	BLOOD CHLORIDE INCREASED	24NOV2014(-2)	12DEC2014(16)	No	MI	MI	NOT	NO	NO	R	No	No
		11	PERSISTENT LOW BUN	INVESTIGATIONS	BLOOD UREA DECREASED	24NOV2014(-2)	12DEC2014(16)	No	MI	MI	NOT	NO	NO	R	No	No
		12	PERSISTENT LOW AST	INVESTIGATIONS	ASPARTATE AMINOTRANSFERASE DECREASED	24NOV2014(-2)	12DEC2014(16)	No	MI	MI	NOT	NO	NO	R	No	No
		2	HYPOALBUMINEMIA	METABOLISM AND NUTRITION DISORDERS	HYPOALBUMINAEMIA	24NOV2014(-2)	15JAN2015(50)	No	MI	MI	NOT	NO	NO	R	No	No
		9	PERSISTENT HIGH GLUCOSE	INVESTIGATIONS	BLOOD GLUCOSE INCREASED	24NOV2014(-2)	27NOV2014(1)	No	MI	MI	NOT	NO	NO	R	No	No

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Cohort 2	3063-003	3	ORAL THRUSH	INFECTIONS AND INFESTATIONS	ORAL CANDIDIASIS	25NOV2014(-1)	12DEC2014(16)	No	MI	MI	NOT	NO	MA	R	No	No
		13	HIGH NEUTROPHILS	INVESTIGATIONS	NEUTROPHIL COUNT INCREASED	27NOV2014(1)	12DEC2014(16)	No	MI	MI	POS	NO	NO	R	No	Yes
		14	LOW MONOCYTES	INVESTIGATIONS	MONOCYTE COUNT DECREASED	27NOV2014(1)	12DEC2014(16)	No	MI	MI	POS	NO	NO	R	No	Yes
		15	HIGH WBC	INVESTIGATIONS	WHITE BLOOD CELL COUNT INCREASED	27NOV2014(1)	12DEC2014(16)	No	MI	MI	POS	NO	NO	R	No	Yes
		16	HIGH GLUCOSE	INVESTIGATIONS	BLOOD GLUCOSE INCREASED	12DEC2014(16)	15JAN2015(50)	No	MI	MI	POS	NO	NO	R	No	Yes
		17	LOW CREATININE	INVESTIGATIONS	BLOOD CREATININE DECREASED	12DEC2014(16)	24JAN2015(59)	No	MI	MI	POS	NO	NO	R	No	Yes
		18	HIGH BASOPHILS	INVESTIGATIONS	BASOPHIL COUNT INCREASED	17DEC2014(21)	15JAN2015(50)	No	MI	MI	POS	NO	NO	R	No	Yes
		19	HIGH MONOCYTES	INVESTIGATIONS	MONOCYTE COUNT INCREASED	15JAN2015(50)	17MAR2015(111)	No	MI	MI	POS	NO	NO	R	No	Yes
		20	HIGH ALKALINE PHOSPHATASE	INVESTIGATIONS	BLOOD ALKALINE PHOSPHATASE INCREASED	15JAN2015(50)	19MAY2015(174)	No	MI	MI	POS	NO	NO	R	No	Yes
		22	HIGH NEUTROPHILS	INVESTIGATIONS	NEUTROPHIL COUNT INCREASED	15JAN2015(50)	17MAR2015(111)	No	MI	MI	POS	NO	NO	R	No	Yes
		4	EOSINOPHILIA	BLOOD AND LYMPHATIC SYSTEM DISORDERS	EOSINOPHILIA	15JAN2015(50)	13FEB2015(79)	No	MI	MI	POS	NO	NO	R	No	Yes
		5	BRONCHIOLITIS	INFECTIONS AND INFESTATIONS	BRONCHIOLITIS	25JAN2015(60)	27JAN2015(62)	Yes -HO	SE	SE	NOT	NO	MA	R	No	Yes
		6	UMBILICAL HERNIA	GASTROINTESTINAL DISORDERS	UMBILICAL HERNIA	17MAR2015(111)		No	MI	MI	UNL	NO	NO	UR	No	Yes

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Grade: IA=Per Investigator Assessment, MI=Mild, MO=Moderate, SE=Severe, LT=Life Threatening, D=Death;
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Listing 16.2.7 Adverse Events

Cohort	Patient ID	AE #	Event	System Organ Class	Preferred Term	Date of Onset (Day)	Resolved or Death Date (Day)	SAE? Specify	---Grade--- CTCAE	IA	Relat	Study Med Action	Treat	Out	WD?	TEAE
Cohort 2	3063-003	7	BRONCHOPNEUMONIA	INFECTIONS AND INFESTATIONS	BRONCHOPNEUMONIA	07APR2015(132)	21APR2015(146)	Yes -HO	SE	SE	UNL	NO	MA	R	No	Yes
		21	PERSISTING HIGH BUN	INVESTIGATIONS	BLOOD UREA INCREASED	19MAY2015(174)		No	MI	MI	POS	NO	NO	UR	No	Yes
Cohort 2	3063-004	1	HYPERCHLOREMIA	METABOLISM AND NUTRITION DISORDERS	HYPERCHLORAEMIA	04JAN2015(-1)	21JAN2015(16)	No	MI	MI	NOT	NO	NO	R	No	No
		16	PERSISTENT LOW NEUTROPHILS	INVESTIGATIONS	NEUTROPHIL COUNT DECREASED	04JAN2015(-1)	06JAN2015(1)	No	MI	MI	NOT	NO	NO	R	No	No
		6	PERSISTENT HIGH GLUCOSE	INVESTIGATIONS	BLOOD GLUCOSE INCREASED	04JAN2015(-1)	06JAN2015(1)	No	MI	MI	NOT	NO	NO	R	No	No
		7	PERSISTENT HIGH BASOPHILS	INVESTIGATIONS	BASOPHIL COUNT INCREASED	04JAN2015(-1)	06JAN2015(1)	No	MI	MI	NOT	NO	NO	R	No	No
		11	HIGH CHLORIDE	INVESTIGATIONS	BLOOD CHLORIDE INCREASED	06JAN2015(1)	21JAN2015(16)	No	MI	MI	POS	NO	NO	R	No	Yes
		2	HYPOALBUMINEMIA	METABOLISM AND NUTRITION DISORDERS	HYPOALBUMINAEMIA	06JAN2015(1)	27FEB2015(53)	No	MI	MI	UNL	NO	NO	R	No	Yes
		3	SMALL EDEMA AT INJECTION SITE	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	INJECTION SITE OEDEMA	08JAN2015(3)	08JAN2015(3)	No	MI	MI	PRO	INT	NO	R	No	Yes
		10	HIGH BASOPHILS	INVESTIGATIONS	BASOPHIL COUNT INCREASED	21JAN2015(16)	27FEB2015(53)	No	MI	MI	POS	NO	NO	R	No	Yes
		4	MONOCYTOSIS	BLOOD AND LYMPHATIC SYSTEM DISORDERS	MONOCYTOSIS	21JAN2015(16)	26JAN2015(21)	No	MI	MI	POS	NO	NO	R	No	Yes

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Listing 16.2.7 Adverse Events

Cohort	Patient ID	AE #	Event	System Organ Class	Preferred Term	Date of Onset (Day)	Resolved or Death Date (Day)	SAE? Specify	---Grade--- CTCAE	IA	Relat	Study Med Action	Treat	Out	WD?	TEAE
Cohort 2	3063-004	9	LOW CREATININE	INVESTIGATIONS	BLOOD CREATININE DECREASED	26JAN2015(21)	29JUN2015(175)	No	MI	MI	POS	NO	NO	R	No	Yes
		5	EOSINOPHILIA	BLOOD AND LYMPHATIC SYSTEM DISORDERS	EOSINOPHILIA	27FEB2015(53)	30APR2015(115)	No	MI	MI	UNL	NO	NO	R	No	Yes
		8	HIGH MONOCYTES	INVESTIGATIONS	MONOCYTE COUNT INCREASED	27FEB2015(53)	30APR2015(115)	No	MI	MI	POS	NO	NO	R	No	Yes
		12	PERSISTING HIGH RBC	INVESTIGATIONS	RED BLOOD CELL COUNT INCREASED	29JUN2015(175)		No	MI	MI	POS	NO	NO	UR	No	Yes
Cohort 3	1068-002	3	CLOUDY CLARITY ON URINALYSIS	RENAL AND URINARY DISORDERS	URINE ABNORMALITY	28FEB2015(1)	15MAR2015(16)	No	MI	MI	UNL	NO	NO	R	No	Yes
		4	LOW SPECIFIC GRAVITY ON URINALYSIS	INVESTIGATIONS	SPECIFIC GRAVITY URINE DECREASED	28FEB2015(1)	15MAR2015(16)	No	MI	MI	UNL	NO	NO	R	No	Yes
		5	1+ LEUKOCYTE ESTERASE ON URINALYSIS	INVESTIGATIONS	URINE LEUKOCYTE ESTERASE POSITIVE	28FEB2015(1)	15MAR2015(16)	No	MI	MI	UNL	NO	NO	R	No	Yes
		6	2+ AMORPHOUS CELLS ON URINE MICROSCOPY	INVESTIGATIONS	URINE ANALYSIS ABNORMAL	28FEB2015(1)	15MAR2015(16)	No	MI	MI	UNL	NO	NO	R	No	Yes
		2	LEFT SKIN BIOPSY SITE REDNESS AND INFLAMMATION	INJURY, POISONING AND PROCEDURAL COMPLICATIONS	PROCEDURAL SITE REACTION	03MAR2015(4)	10MAR2015(11)	No	MI	MI	NOT	NO	MA	R	No	Yes
		1	PICC LINE CLOTTED DURING THIRD DRUG DOSE	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	MEDICAL DEVICE COMPLICATION	06MAR2015(7)	06MAR2015(7)	No	MO	MO	POS	INT	NDT, OM	R	No	Yes

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Listing 16.2.7 Adverse Events

Cohort	Patient ID	AE #	Event	System Organ Class	Preferred Term	Date of Onset (Day)	Resolved or Death Date (Day)	SAE? Specify	---Grade--- CTCAE	IA	Relat	Study Med Action	Treat	Out	WD?	TEAE
Cohort 3	1068-002	7	LOW SODIUM ON CMP	INVESTIGATIONS	BLOOD SODIUM DECREASED	15MAR2015(16)	20MAR2015(21)	No	MI	MI	UNL	NO	NO	R	No	Yes
		8	LOW PLASMA PROTEIN ON CMP	INVESTIGATIONS	PROTEIN TOTAL DECREASED	15MAR2015(16)	20MAR2015(21)	No	MI	MI	UNL	NO	NO	R	No	Yes
		10	TURBID CLARITY ON URINALYSIS	INVESTIGATIONS	URINE ANALYSIS ABNORMAL	20MAR2015(21)	17APR2015(49)	No	MI	MI	UNL	NO	NO	R	No	Yes
		11	2+ AMORPHOUS CELLS ON URINALYSIS	INVESTIGATIONS	URINE ANALYSIS ABNORMAL	20MAR2015(21)	17APR2015(49)	No	MI	MI	UNL	NO	NO	R	No	Yes
		9	HIGH ABSOLUTE EOSINOPHILS ON CBC	INVESTIGATIONS	EOSINOPHIL COUNT INCREASED	20MAR2015(21)	17APR2015(49)	No	MI	MI	UNL	NO	NO	R	No	Yes
		29	CHRONIC NASAL CONGESTION	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	NASAL CONGESTION	23MAR2015(24)	19JUN2015(112)	No	MI	MI	NOT	NO	NDT	R	No	Yes
		16	VOMITING	GASTROINTESTINAL DISORDERS	VOMITING	15APR2015(47)	18APR2015(50)	No	MI	MI	UNL	NO	NO	R	No	Yes
		12	HIGH POTASSIUM ON CMP	INVESTIGATIONS	BLOOD POTASSIUM INCREASED	17APR2015(49)	12AUG2015(166)	No	MI	MI	UNL	NO	NO	R	No	Yes
		13	HIGH SPECIFIC GRAVITY ON URINALYSIS	INVESTIGATIONS	SPECIFIC GRAVITY URINE INCREASED	17APR2015(49)	12AUG2015(166)	No	MI	MI	UNL	NO	NO	R	No	Yes
		14	1+ ALBUMIN ON URINALYSIS	INVESTIGATIONS	ALBUMIN URINE PRESENT	17APR2015(49)	12AUG2015(166)	No	MI	MI	UNL	NO	NO	R	No	Yes
		15	HIGH PLATELETS ON CBC	INVESTIGATIONS	PLATELET COUNT INCREASED	17APR2015(49)	12AUG2015(166)	No	MI	MI	UNL	NO	NO	R	No	Yes
		28	SLIGHT POIKILOCYTOSIS ON CBC	BLOOD AND LYMPHATIC SYSTEM DISORDERS	POIKILOCYTOSIS	17APR2015(49)		No	MI	MI	UNL	NO	NO	UR	No	Yes

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Listing 16.2.7 Adverse Events

Cohort	Patient ID	AE #	Event	System Organ Class	Preferred Term	Date of Onset (Day)	Resolved or Death Date (Day)	SAE? Specify	---Grade--- CTCAE	IA	Relat	Study Med Action	Treat	Out	WD?	TEAE
Cohort 3	1068-002	17	LOW BUN ON CMP	INVESTIGATIONS	BLOOD UREA DECREASED	12AUG2015(166)		No	MI	MI	UNL	NO	NO	UR	No	Yes
		18	HIGH PH ON URINALYSIS	INVESTIGATIONS	PH URINE INCREASED	12AUG2015(166)		No	MI	MI	UNL	NO	NO	UR	No	Yes
		19	HIGH EOSINOPHILS ON CBC	INVESTIGATIONS	EOSINOPHIL COUNT INCREASED	12AUG2015(166)		No	MI	MI	UNL	NO	NO	UR	No	Yes
		20	SLIGHT HYPOCHROMIA ON CBC	BLOOD AND LYMPHATIC SYSTEM DISORDERS	HYPOCHROMASIA	12AUG2015(166)		No	MI	MI	UNL	NO	NO	UR	No	Yes
		21	1-10% MACROCYTES ON CBC	INVESTIGATIONS	RED BLOOD CELL MACROCYTES PRESENT	12AUG2015(166)		No	MI	MI	UNL	NO	NO	UR	No	Yes
		22	1-10% MICROCYTES ON CBC	INVESTIGATIONS	RED BLOOD CELL MACROCYTES PRESENT	12AUG2015(166)		No	MI	MI	UNL	NO	NO	UR	No	Yes
		23	1-10% SPHEROCYTES ON CBC	INVESTIGATIONS	RED BLOOD CELL SPHEROCYTES PRESENT	12AUG2015(166)		No	MI	MI	UNL	NO	NO	UR	No	Yes
		24	1-10% OVALOCYTES ON CBC	INVESTIGATIONS	RED BLOOD CELL ELLIPTOCYTES PRESENT	12AUG2015(166)		No	MI	MI	UNL	NO	NO	UR	No	Yes
		25	1-10% SCHISTOCYTES ON CBC	INVESTIGATIONS	RED BLOOD CELL SCHISTOCYTES PRESENT	12AUG2015(166)		No	MI	MI	UNL	NO	NO	UR	No	Yes
		26	FEW ENLARGED PLATELET MORPHOLOGY ON CBC	INVESTIGATIONS	PLATELET MORPHOLOGY ABNORMAL	12AUG2015(166)		No	MI	MI	UNL	NO	NO	UR	No	Yes
		27	SLIGHT HYPOCHROMIA ON CBC	BLOOD AND LYMPHATIC SYSTEM DISORDERS	HYPOCHROMASIA	12AUG2015(166)		No	MI	MI	UNL	NO	NO	UR	No	Yes

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Listing 16.2.7 Adverse Events

Cohort	Patient ID	AE #	Event	System Organ Class	Preferred Term	Date of Onset (Day)	Resolved or Death Date (Day)	SAE? Specify	---Grade--- CTCAE	IA	Relat	Study Med Action	Treat	Out	WD?	TEAE
Cohort 3	3064-002	16	ONSET OF GASTROOESOPHAGEAL REFLUX	GASTROINTESTINAL DISORDERS	GASTROOESOPHAGEAL REFLUX DISEASE	UK-JUN-2015		No	MI	MI	NOT	NO	MA	UR	No	
		6	PERSISTANT HIGH ALKALINE PHOSPHATASE	INVESTIGATIONS	BLOOD ALKALINE PHOSPHATASE INCREASED	09APR2015(0)	24APR2015(15)	No	MI	MI	NOT	NO	NO	R	No	Yes
		7	PERSISTANT HIGH HEAMOGLOBIN	INVESTIGATIONS	HAEMOGLOBIN INCREASED	09APR2015(0)	24APR2015(15)	No	MI	MI	NOT	NO	NO	R	No	Yes
		8	PERSISTANT HIGH HAEMATOCRIT	INVESTIGATIONS	HAEMATOCRIT INCREASED	09APR2015(0)	24APR2015(15)	No	MI	MI	NOT	NO	NO	R	No	Yes
		1	RAISED SERUM K+ TO 5.8 MMOL/L	INVESTIGATIONS	BLOOD POTASSIUM INCREASED	10APR2015(1)	30APR2015(21)	No	MI	MI	NOT	NO	NO	R	No	Yes
		2	SINGLE EPISODE OF RAISED BILIRUBIN TO 35 MMOL/L	INVESTIGATIONS	BLOOD BILIRUBIN INCREASED	13APR2015(4)	24APR2015(15)	No	MI	MI	NOT	NO	NO	R	No	Yes
		14	URINALYSIS SHOWS TRACE OF PROTEIN	INVESTIGATIONS	PROTEIN URINE	16APR2015(7)	25APR2015(16)	No	MI	MI	NOT	NO	NO	R	No	Yes
		5	URINALYSIS SHOWS TRACE OF BLOOD	INVESTIGATIONS	BLOOD URINE PRESENT	16APR2015(7)	25APR2015(16)	No	MI	MI	NOT	NO	NO	R	No	Yes
		18	NEONATE UNSETTLED	PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	NEONATAL DISORDER	21APR2015(12)	21APR2015(12)	No	MI	MI	UNL	NO	MA	R	No	Yes
		4	RAISED BASOPHIL COUNT IN PERIPHERAL BLOOD	INVESTIGATIONS	BASOPHIL COUNT INCREASED	24APR2015(15)	25APR2015(16)	No	MI	MI	NOT	NO	NO	R	No	Yes

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Listing 16.2.7 Adverse Events

Cohort	Patient ID	AE #	Event	System Organ Class	Preferred Term	Date of Onset (Day)	Resolved or Death Date (Day)	SAE? Specify	---Grade--- CTCAE	IA	Relat	Study Med Action	Treat	Out	WD?	TEAE
Cohort 3	3064-002	19	UNSETTLED AROUND THE TIME OF IMMUNISATION	PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	NEONATAL DISORDER	26MAY2015(47)	27MAY2015(48)	No	MI	MI	NOT	NO	MA	R	No	Yes
		10	LOW HAEMOGLOBIN	INVESTIGATIONS	HAEMOGLOBIN DECREASED	01JUN2015(53)	28SEP2015(172)	No	MI	MI	NOT	NO	NO	R	No	Yes
		11	LOW HAEMATOCRIT	INVESTIGATIONS	HAEMATOCRIT DECREASED	01JUN2015(53)	28SEP2015(172)	No	MI	MI	NOT	NO	NO	R	No	Yes
		3	CHEST INFECTION	INFECTIONS AND INFESTATIONS	LOWER RESPIRATORY TRACT INFECTION	30JUN2015(82)	06JUL2015(88)	Yes -HO	SE	SE	NOT	NO	MA	R	No	Yes
		12	LOW MONOCYTES	INVESTIGATIONS	MONOCYTE COUNT DECREASED	28SEP2015(172)		No	MI	MI	NOT	NO	NO	UR	No	Yes
		13	LOW EOSINOPHILS	INVESTIGATIONS	EOSINOPHIL COUNT DECREASED	28SEP2015(172)		No	MI	MI	NOT	NO	NO	UR	No	Yes
		15	HIGH HAEMOGLOBIN	INVESTIGATIONS	HAEMOGLOBIN INCREASED	28SEP2015(172)		No	MI	MI	NOT	NO	NO	UR	No	Yes
		17	RASH TO CHIN	SKIN AND SUBCUTANEOUS TISSUE DISORDERS	RASH	28SEP2015(172)		No	MI	MI	NOT	NO	NO	UR	No	Yes
		20	EXCESSIVE SALIVATION	GASTROINTESTINAL DISORDERS	SALIVARY HYPERSECRETION	28SEP2015(172)		No	MI	MI	NOT	NO	NO	UR	No	Yes
Siblings	1068-201		NONE REPORTED													
	3063-201		NONE REPORTED													
	3063-202	1	VIRAL INFECTION	INFECTIONS AND INFESTATIONS	VIRAL INFECTION	01DEC2014	11DEC2014	No	MO	MO			NDT	R	No	Yes

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Cohort	Patient ID	AE #	Event	System Organ Class	Preferred Term	Date of Onset (Day)	Resolved or Death Date (Day)	SAE? Specify	---Grade--- CTCAE	IA	Relat	Study Med Action	Treat	Out	WD?	TEAE
Siblings	3063-202	2	UPPER RESPIRATORY INFECTION	INFECTIONS AND INFESTATIONS	UPPER RESPIRATORY TRACT INFECTION	05DEC2014	11DEC2014	No	MO	MO			MA	R	No	Yes
		3	ENLARGED LYMPH NODES IN THE NECK	BLOOD AND LYMPHATIC SYSTEM DISORDERS	LYMPHADENOPATHY	11MAR2015	18MAY2015	No	MI	MI			NO	R	No	Yes
	3064-201		NONE REPORTED													

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Listing 16.2.8.1 Laboratory Results: Biochemistry

Part 1 of 2

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Sodium (mmol/L)	Potassium (mmol/L)	Chloride (mmol/L)	Calcium (mmol/L)	BUN (mg/dL)	Glucose (mg/dL)
Cohort 1	3063-001	M	Baseline	17SEP2013(-1)	136	3.8	106	2.20	23	52
			Day 1	19SEP2013(1)	137	4.3	107	2.45	16	75
			Unscheduled	20SEP2013(2)	UNK	UNK	UNK	UNK	UNK	UNK
			Day 16	04OCT2013(16)	131 L CS	4.0	101	2.51	6 L NCS	100 H NCS
			Day 21	09OCT2013(21)	129 L CS	4.2	100	2.55	9	102 H NCS
			Unscheduled	19NOV2013(62)	UNK	UNK	UNK	UNK	UNK	UNK
			Month 2	20NOV2013(63)	132	4.3	102	2.45	4	96
			Unscheduled	16JAN2014(120)	134	3.8	102	2.47	4	UNK
			Month 6	24MAR2014(187)	133	4.3	105	2.47	4	93
				21SEP2015(733)	14	4.1	102	2.44	34 NCS	
Cohort 1	1012-001	M	Baseline	26NOV2013(-6)	139	4.7	102	2.89 H NCS	12	82
			Day 1	03DEC2013(1)	139	4.0	104	2.57	10	94
			Day 16	18DEC2013(16)	139	3.9	101	2.62	6	93
			Day 21	23DEC2013(21)	135	5.1	98	2.74 H NCS	8	86
			Month 2	22JAN2014(51)	137	5.3	103	2.57	<5 NCS	100
			Month 6	30MAY2014(179)	140	4.4	106	2.62	5	80
Cohort 1	1068-001	M	Baseline	03MAR2014(-2)	134 L NCS	4.2	106	2.42	4 L NCS	78
			Day 1	06MAR2014(1)	138	4.8	107	2.54	3 L NCS	98
			Day 16	21MAR2014(16)	138	5.3 H NCS	108	2.52	7 L NCS	97
			Day 21	26MAR2014(21)	137	ND	107	2.59	7 L NCS	85
			Month 2	22APR2014(48)	140	5.9 H NCS	110	2.52	9	80
			Month 2	23APR2014(49)	139	ND	109	2.62	9	89
			Month 6	26AUG2014(174)	139	4.1	107	2.50	11	98
				24FEB2016(721)	136	4.7	108	2.30	14	
Cohort 2	3064-001	M	Baseline	09MAY2014(0)	137	5.4	103	2.70	1	ND
			Day 1	10MAY2014(1)	133	ND	107	2.61	2	ND

UNK=Unknown, ND=Not Done, H=Above Normal Range, L=Below Normal Range, CS=Clinically Significant, NCS=Not Clinically Significant

Listing 16.2.8.1 Laboratory Results: Biochemistry
Part 1 of 2

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Sodium (mmol/L)	Potassium (mmol/L)	Chloride (mmol/L)	Calcium (mmol/L)	BUN (mg/dL)	Glucose (mg/dL)
Cohort 2	3064-001	M	Unscheduled	13MAY2014(4)	138	4.8	101	2.72 H NCS	2	ND
			Unscheduled	16MAY2014(7)	ND	ND	ND	2.74 H NCS	ND	ND
			Unscheduled	19MAY2014(10)	ND	ND	ND	2.64	ND	ND
			Day 16	25MAY2014(16)	136	4.5	104	2.59	3	ND
			Day 21	30MAY2014(21)	135	4.6	102	2.75 H NCS	3	ND
			Month 2	30JUN2014(52)	135	4.5	102	2.54	6	85
			Month 6	03NOV2014(178)	136	4.1	104	2.57	10	90
Cohort 2	3005-001	M	Baseline	31JUL2014(-4)	138	5.4	107 H NCS	2.58	7	85
			Day 1	05AUG2014(1)	135	5.6	108 H NCS	2.49	7	92
			Day 16	20AUG2014(16)	137	5.4 NCS	107 H NCS	2.57	5	101 H NCS
			Day 21	25AUG2014(21)	136	5.0 NCS	106	2.56	ND	83
			Month 2	08SEP2014(35)	136	5.3 NCS	107 H NCS	2.60	8	90
			Month 6	12JAN2015(161)	137	4.8	105	2.60	8	99
Cohort 2	3063-002	F	Baseline	29OCT2014(-4)	139	4.7	107	2.70 H NCS	18	87 H NCS
			Day 1	03NOV2014(1)	137	4.4	106	2.49	15	105 H NCS
			Unscheduled	12NOV2014(10)	134	5.2	109 H NCS	2.39	12	125 H NCS
			Day 16	18NOV2014(16)	135	4.4	109 H NCS	2.54	18	90 H NCS
			Day 21	23NOV2014(21)	134	5.1	103	2.57	21	81
			Month 2	18DEC2014(46)	134	5.0	105	2.49	18	89
			Month 6	21APR2015(170)	139	4.7	111 H CS	2.48	17	97
Cohort 2	3063-003	M	Baseline	24NOV2014(-2)	141	4.0	109 H NCS	2.43	7 L NCS	91 H NCS
			Day 1	27NOV2014(1)	142	4.6	111 H NCS	2.37	4 L NCS	76
			Day 16	12DEC2014(16)	137	4.5	103	2.50	9	113 H NCS
			Day 21	17DEC2014(21)	137	4.7	106	2.44	14	85 H NCS
			Month 2	15JAN2015(50)	138	4.9	105	2.51	9	99
			Unscheduled	24JAN2015(59)	139	5.2 H CS	102	2.45	12 L NCS	118 H NCS
			Unscheduled	17MAR2015(111)	136	4.5	107	UNK	17	UNK
			Unscheduled	12APR2015(137)	139	4.5	104	2.47	6 L NCS	111 H NCS
			Unscheduled	13APR2015(138)	137	4.2	99	UNK	11 L NCS	104
			Month 6	19MAY2015(174)	137	4.2	106	2.51	31 H NCS	92
Cohort 2	3063-004	M	Baseline	04JAN2015(-1)	138	4.1	112 H CS	2.19	21	85 H NCS

UNK=Unknown, ND=Not Done, H=Above Normal Range, L=Below Normal Range, CS=Clinically Significant, NCS=Not Clinically Significant

Listing 16.2.8.1 Laboratory Results: Biochemistry
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Cohort	Patient ID	Gender	Visit	Study Date (Day)	Sodium (mmol/L)	Potassium (mmol/L)	Chloride (mmol/L)	Calcium (mmol/L)	BUN (mg/dL)	Glucose (mg/dL)
Cohort 2	3063-004	M	Day 1	06JAN2015(1)	138	4.3	109 H NCS	2.35	15	78
			Day 16	21JAN2015(16)	136	4.7	102	2.57	15	79
			Day 21	26JAN2015(21)	135	4.4	100	2.59	13	79
			Month 2	27FEB2015(53)	136	4.9	104	2.58	12	91
			Month 6	29JUN2015(175)	135	4.2	102	2.53	24	98
Cohort 3	1068-002	M	Baseline	25FEB2015(-2)	136	ND	103	2.40	5 L NCS	104
			Baseline	26FEB2015(-1)	141	5.6 H NCS	108	2.64	4 L NCS	107
			Day 1	28FEB2015(1)	138	ND	107	2.50	4 L NCS	88
			Unscheduled	28FEB2015(1)	ND	5.6 H NCS	ND	ND	ND	ND
			Day 16	15MAR2015(16)	134 L NCS	4.8	104	2.42	12	87
			Day 21	20MAR2015(21)	140	4.4	108	2.52	12	102
			Month 2	17APR2015(49)	136	5.3 H NCS	104	2.62	10	103
			Month 6	12AUG2015(166)	139	3.9	105	2.64	7 L NCS	92
Cohort 3	3064-002	M	Baseline	09APR2015(0)	141	ND	105	2.45	4	81
			Day 1	10APR2015(1)	139	5.8 H NCS	106	2.67	4	87
			Unscheduled	13APR2015(4)	140	5.7 H NCS	ND	2.63	3	ND
			Unscheduled	24APR2015(15)	141	5.4 H NCS	ND	2.61	5	ND
			Day 16	25APR2015(16)	139	5.4 H NCS	106	ND	6	103
			Day 21	30APR2015(21)	139	4.8	105	2.52	8	87
			Month 2	01JUN2015(53)	138	4.4	ND	2.62	5	74
			Month 6	28SEP2015(172)	140	4.8	107	2.63	9	ND

UNK=Unknown, ND=Not Done, H=Above Normal Range, L=Below Normal Range, CS=Clinically Significant, NCS=Not Clinically Significant

Listing 16.2.8.1 Laboratory Results: Biochemistry

Part 2 of 2

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Creatinine (mg/dL)	Total Protein (g/L)	Albumin (g/L)	AST (SGOT) (U/L)	ALT (SGPT) (U/L)	Alkaline Phosphatase (U/L)
Cohort 1	3063-001	M	Baseline	17SEP2013(-1)	0.55	55	33.6	80	9	160
			Day 1	19SEP2013(1)	0.34	55	33.1	29	9	147
			Unscheduled	20SEP2013(2)	0.29 L NCS	UNK	UNK	UNK	UNK	UNK
			Day 16	04OCT2013(16)	0.23 L NCS	56	31.2 L CS	30	12	260
			Day 21	09OCT2013(21)	0.25 L NCS	58	30.1 L CS	42	14	315
			Unscheduled	19NOV2013(62)	0.20	UNK	UNK	UNK	UNK	UNK
			Month 2	20NOV2013(63)	0.19	58	36.6 L CS	37	14	393
			Unscheduled	16JAN2014(120)	0.18	63	42.9	43	14	354
			Month 6	24MAR2014(187)	0.15 L NCS	67	43.1	45	14	352
				21SEP2015(733)	0.35	67	44.3	39	17	252
Cohort 1	1012-001	M	Baseline	26NOV2013(-6)	0.48	62	35.0	29	21	97
			Day 1	03DEC2013(1)	0.33	51	32.0	31	22	134
			Day 16	18DEC2013(16)	<0.30 L NCS	54	34.0	31	32	191
			Day 21	23DEC2013(21)	0.33	63	40.0	40	33	228
			Month 2	22JAN2014(51)	<0.30 L NCS	61	37.0	35	27	195
			Month 6	30MAY2014(179)	<0.30 L NCS	64	41.0	38	25	143
Cohort 1	1068-001	M	Baseline	03MAR2014(-2)	0.40	48 L NCS	32.0	39	20	146
			Day 1	06MAR2014(1)	0.40	52 L NCS	33.0	38	24	167
			Day 16	21MAR2014(16)	0.20	53 L NCS	36.0	31	27	235
			Day 21	26MAR2014(21)	0.30	56	37.0	ND	35	273
			Month 2	22APR2014(48)	0.20	58	37.0	94 H NCS	90 H NCS	220
			Month 2	23APR2014(49)	0.20	58	36.0	ND	64 H NCS	196
			Month 6	26AUG2014(174)	0.30	60	43.0	56	30	179
				24FEB2016(721)	0.20	65	41.0	57	24	172
Cohort 2	3064-001	M	Baseline	09MAY2014(0)	0.46	58	30.0 L NCS	35	17	135
			Day 1	10MAY2014(1)	0.35	61	27.0 L NCS	46	14	124
			Unscheduled	13MAY2014(4)	0.41 H NCS	60	26.0 L NCS	17	9	116
			Unscheduled	16MAY2014(7)	ND	ND	24.0 L NCS	ND	ND	ND
			Unscheduled	19MAY2014(10)	ND	ND	24.0 L NCS	ND	ND	ND
			Day 16	25MAY2014(16)	0.35	50	25.0 L NCS	26	12	172
			Day 21	30MAY2014(21)	0.35	53	28.0 L NCS	27	12	207

UNK=Unknown, ND=Not Done, H=Above Normal Range, L=Below Normal Range, CS=Clinically Significant, NCS=Not Clinically Significant

Listing 16.2.8.1 Laboratory Results: Biochemistry
Part 2 of 2

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Creatinine (mg/dL)	Total Protein (g/L)	Albumin (g/L)	AST (SGOT) (U/L)	ALT (SGPT) (U/L)	Alkaline Phosphatase (U/L)
Cohort 2	3064-001	M	Month 2	30JUN2014(52)	0.33	58	31.0 L NCS	26	12	198
			Month 6	03NOV2014(178)	0.42 H NCS	67	37.0	40	18	168
Cohort 2	3005-001	M	Baseline	31JUL2014(-4)	0.24	59	35.5 L NCS	28	20	233
			Day 1	05AUG2014(1)	0.20	57	32.0 L NCS	37	18	319 H NCS
			Day 16	20AUG2014(16)	0.23	57	35.8	33	15	368 H NCS
			Day 21	25AUG2014(21)	0.23	53	35.1	25	13	340 H NCS
			Month 2	08SEP2014(35)	0.21	58	39.1	30	19	393 H NCS
			Month 6	12JAN2015(161)	0.17	66	40.6	38	23	272
Cohort 2	3063-002	F	Baseline	29OCT2014(-4)	0.41	50	35.8 L CS	32	6	207
			Day 1	03NOV2014(1)	0.35	49	35.8 L CS	39	9	227
			Unscheduled	12NOV2014(10)	0.25 L NCS	54	UNK	UNK	UNK	UNK
			Day 16	18NOV2014(16)	0.30 L NCS	51	34.4 L CS	38	9	211
			Day 21	23NOV2014(21)	0.21 L NCS	44	38.7	42	16	286
			Month 2	18DEC2014(46)	0.24 L NCS	49	38.3	30	12	385
			Month 6	21APR2015(170)	0.24	58	41.1	35	13	349
Cohort 2	3063-003	M	Baseline	24NOV2014(-2)	0.41	48	32.1 L CS	18 L NCS	7	165
			Day 1	27NOV2014(1)	0.36	52	32.9 L CS	18 L NCS	9	193
			Day 16	12DEC2014(16)	0.27 L NCS	54	34.3 L CS	20	11	360
			Day 21	17DEC2014(21)	0.29 L NCS	55	35.5 L CS	41	17	390
			Month 2	15JAN2015(50)	0.22 L NCS	59	39.1	28	13	541 H NCS
			Unscheduled	24JAN2015(59)	0.20	65	UNK	34	16	UNK
			Unscheduled	17MAR2015(111)	0.24	58	UNK	33	23	UNK
			Unscheduled	12APR2015(137)	0.20	58 L CS	UNK	36	21	UNK
			Unscheduled	13APR2015(138)	0.20	UNK	UNK	UNK	19	UNK
			Month 6	19MAY2015(174)	0.23	57	40.3	28	22	246
Cohort 2	3063-004	M	Baseline	04JAN2015(-1)	0.44	48	34.0	37	14	148
			Day 1	06JAN2015(1)	0.44	50	34.5 L CS	27	18	176
			Day 16	21JAN2015(16)	0.31	51	32.6 L CS	29	20	294
			Day 21	26JAN2015(21)	0.29 L NCS	52	34.1 L CS	28	19	281
			Month 2	27FEB2015(53)	0.24 L NCS	57	38.8	39	38	283

UNK=Unknown, ND=Not Done, H=Above Normal Range, L=Below Normal Range, CS=Clinically Significant, NCS=Not Clinically Significant

Listing 16.2.8.1 Laboratory Results: Biochemistry
Part 2 of 2

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Creatinine (mg/dL)	Total Protein (g/L)	Albumin (g/L)	AST (SGOT) (U/L)	ALT (SGPT) (U/L)	Alkaline Phosphatase (U/L)
Cohort 2	3063-004	M	Month 6	29JUN2015(175)	0.26	63	44.7	35	18	278
Cohort 3	1068-002	M	Baseline	25FEB2015(-2)	0.30	57	38.0	ND	ND	ND
			Baseline	26FEB2015(-1)	0.40	62	37.0	46	23	124
			Day 1	28FEB2015(1)	0.40	61	36.0	ND	28	123
			Unscheduled	28FEB2015(1)	ND	ND	ND	ND	ND	ND
			Day 16	15MAR2015(16)	0.30	51 L NCS	33.0	21	18	161
			Day 21	20MAR2015(21)	0.20	55	37.0	23	18	166
			Month 2	17APR2015(49)	0.30	65	38.0	34	30	203
			Month 6	12AUG2015(166)	0.20	65	42.0	41	22	196
Cohort 3	3064-002	M	Baseline	09APR2015(0)	0.38 L NCS	ND	34.0	ND	ND	332 H NCS
			Day 1	10APR2015(1)	0.44	58	33.0	40	18	323 H NCS
			Unscheduled	13APR2015(4)	0.42	56	30.0	ND	18	337 H NCS
			Unscheduled	24APR2015(15)	0.35	53	31.0	ND	18	385
			Day 16	25APR2015(16)	0.40	53	31.0	ND	19	388
			Day 21	30APR2015(21)	0.38	52	32.0	28	21	405
			Month 2	01JUN2015(53)	0.35	56	32.0	ND	23	426
			Month 6	28SEP2015(172)	0.37	63	39.0	44	33	395

UNK=Unknown, ND=Not Done, H=Above Normal Range, L=Below Normal Range, CS=Clinically Significant, NCS=Not Clinically Significant

Listing 16.2.8.2 Laboratory Results: Hematology

Part 1 of 2

Cohort	Patient ID	Gender	Visit	Study Date (Day)	WBC (x10^3/uL)	RBC (x10^6/uL)	Hemoglobin (g/dL)	Hematocrit (%)	Platelets (x10^3/uL)
Cohort 1	3063-001	M	Baseline	17SEP2013(-1)	10.60	4.67	19.1	54.8 H NCS	162 L NCS
			Day 1	19SEP2013(1)	8.48	4.93	18.9	56.6 H NCS	165 L NCS
			Day 16	04OCT2013(16)	9.39	4.42	15.8 H NCS	44.9	331
			Day 21	09OCT2013(21)	9.01	4.20	14.9	42.3	308
			Month 2	20NOV2013(63)	9.34	3.44	10.7	33.6	503
			Unscheduled	16JAN2014(120)	10.00	4.34	11.2	33.4	419
			Month 6	24MAR2014(187)	10.83	5.25 H NCS	11.7	38.1 H NCS	366
				21SEP2015(733)	10.92	4.75	12.0	35.9	347
Cohort 1	1012-001	M	Baseline	26NOV2013(-6)	10.00	5.63	18.3	53.1	187
			Day 1	03DEC2013(1)	10.60	4.51	14.5	42.6	270
			Day 16	18DEC2013(16)	8.20	3.99	11.9 L NCS	35.0 L NCS	171
			Day 21	23DEC2013(21)	11.00	4.25	12.7	36.7	278
			Month 2	22JAN2014(51)	7.70	3.89	10.3	30.9 L NCS	326
			Month 6	30MAY2014(179)	6.70	5.16 H NCS	11.0	33.7	241
Cohort 1	1068-001	M	Baseline	03MAR2014(-2)	9.50	4.12	14.4	42.3	416
			Day 1	06MAR2014(1)	14.30	4.11	14.6	41.8	495 H NCS
			Day 16	21MAR2014(16)	12.00	3.71	12.4	35.9	408
			Day 21	26MAR2014(21)	15.00	3.82	12.6	36.1	385
			Month 2	22APR2014(48)	12.10	3.42	10.5	30.8	468 H NCS
			Month 6	26AUG2014(174)	10.60	4.47	11.1	33.6	385
				24FEB2016(721)	4.70 L	4.03	10.7 L	31.2 L	311
Cohort 2	3064-001	M	Baseline	09MAY2014(0)	21.10 H NCS	4.58	15.0	45.0	504 H NCS
			Day 1	10MAY2014(1)	41.40 H CS	4.40	14.0	44.0	454
			Unscheduled	12MAY2014(3)	26.00 H CS	4.36	15.0	43.0	475
			Unscheduled	13MAY2014(4)	19.30 H NCS	3.97	13.0	39.0	618 H NCS
			Unscheduled	16MAY2014(7)	16.90	4.02	13.0	39.0	738 H NCS
			Unscheduled	19MAY2014(10)	20.80 H NCS	4.16	14.0	40.0	797 H NCS
			Day 16	25MAY2014(16)	12.90	3.58	11.0 L NCS	35.0	580 H NCS
			Day 21	30MAY2014(21)	14.50	3.54	11.0 L NCS	34.0	533 H NCS
			Month 2	30JUN2014(52)	13.50	3.20	10.0 L NCS	29.0 L NCS	598 H NCS
			Month 6	03NOV2014(178)	13.70	4.50	11.0	32.0	511 H NCS

ND=Not Done, H=Above Normal Range, L=Below Normal Range, CS=Clinically Significant, NCS=Not Clinically Significant

Listing 16.2.8.2 Laboratory Results: Hematology
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Cohort	Patient ID	Gender	Visit	Study Date (Day)	WBC (x10^3/uL)	RBC (x10^6/uL)	Hemoglobin (g/dL)	Hematocrit (%)	Platelets (x10^3/uL)
Cohort 2	3005-001	M	Baseline	31JUL2014(-4)	8.00	3.04	9.9 L NCS	28.4 L NCS	309
			Day 1	05AUG2014(1)	7.40	2.72 L NCS	8.7 L NCS	24.9 L NCS	230
			Day 16	20AUG2014(16)	7.00	3.04 L NCS	9.4	27.4 L NCS	356
			Day 21	25AUG2014(21)	5.90	2.75 L NCS	8.1 L NCS	23.9 L NCS	313
			Month 2	08SEP2014(35)	7.60	3.55 L NCS	10.1	30.0	199
			Month 6	12JAN2015(161)	7.50	4.90 H NCS	12.5 H NCS	36.3 H NCS	209
Cohort 2	3063-002	F	Baseline	29OCT2014(-4)	11.09	4.06 L NCS	14.7	42.1	352
			Day 1	03NOV2014(1)	11.66	4.18	14.8	42.0	414
			Unscheduled	12NOV2014(10)	18.73 H CS	3.49	12.0	33.1	621 H CS
			Unscheduled	14NOV2014(12)	9.79	3.48	11.8	34.2	630 H CS
			Day 16	18NOV2014(16)	12.52	3.35	11.3	32.8	566
			Day 21	23NOV2014(21)	13.28	3.64	12.1 H NCS	34.7	513
			Month 2	18DEC2014(46)	8.92	3.43	10.6	31.2	406
			Month 6	21APR2015(170)	14.61 H CS	4.85	12.7	38.3 H NCS	372
Cohort 2	3063-003	M	Baseline	24NOV2014(-2)	10.98	3.70 L CS	12.0 L CS	35.0 L CS	307
			Day 1	27NOV2014(1)	17.09 H NCS	3.45 L CS	11.3 L CS	32.5 L CS	391
			Day 16	12DEC2014(16)	13.15	3.01 L CS	9.2 L CS	26.9 L CS	462
			Day 21	17DEC2014(21)	12.26	2.93 L CS	8.7 L CS	25.7 L CS	319
			Month 2	15JAN2015(50)	14.51	2.88 L CS	8.1 L CS	23.9 L CS	468
			Unscheduled	24JAN2015(59)	14.06	3.18	8.7 L CS	25.1 L CS	567 H CS
			Unscheduled	13FEB2015(79)	12.59	3.55	8.9 L CS	27.6 L CS	625 H CS
			Unscheduled	17MAR2015(111)	12.98	3.78	9.5 L CS	28.6	440
			Unscheduled	12APR2015(137)	7.17	3.86	9.7 L CS	27.9 L CS	196
			Unscheduled	13APR2015(138)	7.46	4.15	10.0	29.7	249
			Month 6	19MAY2015(174)	10.12	4.08	10.1	29.8 L CS	291
Cohort 2	3063-004	M	Baseline	04JAN2015(-1)	7.02 L CS	5.09	17.4	50.3	279
			Day 1	06JAN2015(1)	10.79	4.95	17.2	49.7	303
			Day 16	21JAN2015(16)	11.20	4.37	14.5	42.4	412
			Day 21	26JAN2015(21)	11.10	4.01	13.4	37.9	376
			Month 2	27FEB2015(53)	12.47	3.39	9.9	29.5	545
			Unscheduled	30APR2015(115)	9.28	4.69	11.6	34.3	463
			Month 6	29JUN2015(175)	8.70	4.88 H NCS	11.3	34.3	371

ND=Not Done, H=Above Normal Range, L=Below Normal Range, CS=Clinically Significant, NCS=Not Clinically Significant

Listing 16.2.8.2 Laboratory Results: Hematology
Part 1 of 2

Cohort	Patient ID	Gender	Visit	Study Date (Day)	WBC (x10^3/uL)	RBC (x10^6/uL)	Hemoglobin (g/dL)	Hematocrit (%)	Platelets (x10^3/uL)
Cohort 3	1068-002	M	Baseline	25FEB2015(-2)	16.80	5.31	17.1	49.2	461 H NCS
			Day 1	28FEB2015(1)	13.40	4.87	15.4	45.3	444 H NCS
			Day 16	15MAR2015(16)	9.20	3.74	11.8	34.2	372
			Day 21	20MAR2015(21)	11.20	3.49	10.9	31.6	372
			Month 2	17APR2015(49)	10.50	3.77	11.0	32.9	501 H NCS
			Month 6	12AUG2015(166)	9.50	4.33	11.3	33.7	374
Cohort 3	3064-002	M	Baseline	09APR2015(0)	11.20	5.45	18.0 H NCS	56.0 H NCS	390
			Day 1	10APR2015(1)	13.00	5.46	18.0 H NCS	56.0 H NCS	325
			Unscheduled	24APR2015(15)	11.90	4.47	15.0	44.0	310
			Day 16	25APR2015(16)	8.60	4.19	14.0	42.0	354
			Day 21	30APR2015(21)	11.40	3.88	13.0	38.0	348
			Month 2	01JUN2015(53)	7.70	3.51	11.0 L NCS	32.0 L NCS	491
			Month 6	28SEP2015(172)	8.80	4.60	12.0 H NCS	37.0	445

ND=Not Done, H=Above Normal Range, L=Below Normal Range, CS=Clinically Significant, NCS=Not Clinically Significant

Listing 16.2.8.2 Laboratory Results: Hematology

Part 2 of 2

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Neutrophils (x10^3/uL)	Lymphocytes (x10^3/uL)	Monocytes (x10^3/uL)	Eosinophils (x10^3/uL)	Basophils (x10^3/uL)
Cohort 1	3063-001	M	Baseline	17SEP2013(-1)	7.10 H NCS	2.30	0.50 L NCS	0.54	0.06
			Day 1	19SEP2013(1)	3.00	3.60	1.20	0.70 H NCS	0.02
			Day 16	04OCT2013(16)	2.40	5.00	1.30	0.67	0.03
			Day 21	09OCT2013(21)	2.90	4.10	0.60	0.50	0.02
			Month 2	20NOV2013(63)	2.10	5.89	0.89	0.43	0.03
			Unscheduled	16JAN2014(120)	2.40	6.60	0.50	0.49	0.03
			Month 6	24MAR2014(187)	2.70	5.40	0.20 L NCS	2.40 H CS	0.00 L NCS
				21SEP2015(733)	2.50	6.10 CS	0.70	0.50	0.10 NCS
Cohort 1	1012-001	M	Baseline	26NOV2013(-6)	2.26	5.43	1.68	0.52	0.09
			Day 1	03DEC2013(1)	4.03	4.35	1.65	0.60	0.03
			Day 16	18DEC2013(16)	1.79	4.19	1.41	0.71	0.07
			Day 21	23DEC2013(21)	2.08	6.50	1.37	1.00	0.05
			Month 2	22JAN2014(51)	1.12	3.92	1.73	0.73	0.24
			Month 6	30MAY2014(179)	0.82 L NCS	4.54	1.02	0.28	0.05
Cohort 1	1068-001	M	Baseline	03MAR2014(-2)	2.64	5.10	1.26 H NCS	0.36	0.07
			Day 1	06MAR2014(1)	4.29	6.86	2.00 H NCS	0.86	ND
			Day 16	21MAR2014(16)	1.92	7.68	1.80 H NCS	0.60	ND
			Day 21	26MAR2014(21)	2.10 L NCS	9.75	1.95 H NCS	0.75	ND
			Month 2	22APR2014(48)	4.48	5.81	1.45 H NCS	0.12	ND
			Month 6	26AUG2014(174)	1.70	7.31	0.42	0.32	0.11
				24FEB2016(721)	1.97	2.30	0.28	0.09	ND
Cohort 2	3064-001	M	Baseline	09MAY2014(0)	9.20	7.50	3.30 H NCS	0.60	0.50 H NCS
			Day 1	10MAY2014(1)	28.98 H CS	10.35 H NCS	1.66 H NCS	0.41	ND
			Unscheduled	12MAY2014(3)	15.80 H NCS	5.30	3.20 H NCS	1.00	0.80 H NCS
			Unscheduled	13MAY2014(4)	10.80 H NCS	4.80	2.60 H NCS	0.60	0.50 H NCS
			Unscheduled	16MAY2014(7)	6.60	6.50	2.60 H NCS	0.80	0.40 H NCS
			Unscheduled	19MAY2014(10)	9.70	6.70	2.90 H NCS	0.90	0.60 H NCS
			Day 16	25MAY2014(16)	5.90	4.50	1.70 H NCS	0.60	0.30 H NCS
			Day 21	30MAY2014(21)	5.60	6.80	1.30	0.60	0.20
			Month 2	30JUN2014(52)	6.00	5.60	1.20	0.60	0.20
			Month 6	03NOV2014(178)	5.50	6.90	0.80	0.30	0.20

ND=Not Done, H=Above Normal Range, L=Below Normal Range, CS=Clinically Significant, NCS=Not Clinically Significant

Listing 16.2.8.2 Laboratory Results: Hematology
Part 2 of 2

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Neutrophils (x10^3/uL)	Lymphocytes (x10^3/uL)	Monocytes (x10^3/uL)	Eosinophils (x10^3/uL)	Basophils (x10^3/uL)
Cohort 2	3005-001	M	Baseline	31JUL2014(-4)	22.00 H NCS	62.00 H NCS	12.00 H NCS	3.00 H NCS	0.00
			Day 1	05AUG2014(1)	21.00 H NCS	64.00 H NCS	11.00 H NCS	3.00 H NCS	0.00
			Day 16	20AUG2014(16)	18.00 H NCS	70.00 H NCS	10.00 H NCS	2.00 H NCS	0.00
			Day 21	25AUG2014(21)	22.00 H NCS	68.00 H NCS	7.00 H NCS	3.00 H NCS	0.00
			Month 2	08SEP2014(35)	1.20	5.40	0.60	0.40 H NCS	0.00
			Month 6	12JAN2015(161)	22.00 H NCS	63.00 H NCS	9.00 H NCS	6.00 H NCS	0.00
Cohort 2	3063-002	F	Baseline	29OCT2014(-4)	2.90	6.80	0.40 L NCS	0.36	0.04
			Day 1	03NOV2014(1)	3.80	5.70	1.30	0.80 H CS	0.04
			Unscheduled	12NOV2014(10)	7.80 H CS	7.90	2.60 H CS	0.20	0.20 H NCS
			Unscheduled	14NOV2014(12)	3.40	4.80	1.20	0.40	UNK
			Day 16	18NOV2014(16)	2.90	6.90	1.30 H NCS	0.50	0.10 H NCS
			Day 21	23NOV2014(21)	2.10	8.50	0.90	0.10	0.04
			Month 2	18DEC2014(46)	1.20 L NCS	7.00	0.50	0.20	0.02
			Month 6	21APR2015(170)	2.80	10.40 H CS	0.90	0.30	0.10 H NCS
Cohort 2	3063-003	M	Baseline	24NOV2014(-2)	4.40	4.70	0.90	0.50	0.04
			Day 1	27NOV2014(1)	11.20 H NCS	4.80	0.50 L NCS	0.50	0.04
			Day 16	12DEC2014(16)	4.90	6.20	1.20	0.40	0.04
			Day 21	17DEC2014(21)	3.10	7.50	0.90	0.10	0.20 H NCS
			Month 2	15JAN2015(50)	4.50 H NCS	7.50	1.20 H NCS	0.70 H CS	0.04
			Unscheduled	24JAN2015(59)	9.90 H CS	3.41	0.57	0.15	0.03
			Unscheduled	13FEB2015(79)	3.54	7.89	0.85 H NCS	0.23	0.09
			Unscheduled	17MAR2015(111)	3.60	7.30	1.00	0.30	UNK
			Unscheduled	12APR2015(137)	1.96	4.68	0.52	0.00 L NCS	0.01
			Unscheduled	13APR2015(138)	2.61	4.03	0.73	0.06	0.03
			Month 6	19MAY2015(174)	2.54	6.66	0.63	0.27	0.02
Cohort 2	3063-004	M	Baseline	04JAN2015(-1)	1.50 L NCS	3.20	0.90	0.60	0.20 H NCS
			Day 1	06JAN2015(1)	5.10	4.50	0.80	0.30	0.08
			Day 16	21JAN2015(16)	2.60	4.70	2.80 H CS	0.40	0.10 H NCS
			Day 21	26JAN2015(21)	2.70	5.60	1.20	0.70	0.10 H NCS
			Month 2	27FEB2015(53)	3.60	6.90	1.10 H NCS	0.70 H CS	0.02
			Unscheduled	30APR2015(115)	2.00	6.20	0.60	0.40	UNK
			Month 6	29JUN2015(175)	2.30	5.40	0.60	0.30	0.06

ND=Not Done, H=Above Normal Range, L=Below Normal Range, CS=Clinically Significant, NCS=Not Clinically Significant

Listing 16.2.8.2 Laboratory Results: Hematology
Part 2 of 2

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Neutrophils (x10^3/uL)	Lymphocytes (x10^3/uL)	Monocytes (x10^3/uL)	Eosinophils (x10^3/uL)	Basophils (x10^3/uL)
Cohort 3	1068-002	M	Baseline	25FEB2015(-2)	8.90	4.70	2.52 H NCS	0.34	ND
			Day 1	28FEB2015(1)	4.42	7.10	1.34 H NCS	0.40	ND
			Day 16	15MAR2015(16)	1.92	5.48	1.22 H NCS	0.41	0.08
			Day 21	20MAR2015(21)	4.01	5.08	1.12 H NCS	0.87	0.06
			Month 2	17APR2015(49)	3.36	4.83	0.42	0.21	ND
			Month 6	12AUG2015(166)	2.28	4.94	0.76 H NCS	1.33 H NCS	ND
Cohort 3	3064-002	M	Baseline	09APR2015(0)	4.20	5.60	1.10	0.30	0.10
			Day 1	10APR2015(1)	5.30	5.60	1.40	0.50	0.20
			Unscheduled	24APR2015(15)	4.00	6.00	1.20	0.50	0.30 H NCS
			Day 16	25APR2015(16)	2.70	4.80	0.60	0.30	0.10
			Day 21	30APR2015(21)	4.70	5.60	0.80	0.30	0.10
			Month 2	01JUN2015(53)	2.20	4.40	0.70	0.30	0.10
			Month 6	28SEP2015(172)	2.70	5.30	0.40 L NCS	0.20 L NCS	0.10

ND=Not Done, H=Above Normal Range, L=Below Normal Range, CS=Clinically Significant, NCS=Not Clinically Significant

Listing 16.2.8.3 Laboratory Results: Urinalysis

Part 1 of 2

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Urinalysis							
					Protein	Glucose	Ketones	Nitrite	Bilirubin	Blood	Leukocytes	Urobilinogen
Cohort 1	3063-001	M	Baseline	17SEP2013(-1)	+1 NCS	0	0	0	0	0	+1 NCS	0
			Day 1	19SEP2013(1)	0	0	0	0	+1 NCS	0	0	0
			Day 16	04OCT2013(16)	0	0	0	0	0	0	0	0
			Day 21	09OCT2013(21)	0	0	0	0	0	0	0	0
			Month 2	19NOV2013(62)	0	0	0	0	0	0	0	0
			Month 6	24MAR2014(187)	0	0	0	0	0	0	0	0
				21SEP2015(733)	0	0	0	0	0	0	0	0
Cohort 1	1012-001	M	Baseline	27NOV2013(-5)	0	0	0	0	0	+1 NCS	0	0
			Day 1	03DEC2013(1)	0	0	0	0	0	0	0	0
			Day 16	18DEC2013(16)	0	0	0	0	0	0	0	0
			Day 21	23DEC2013(21)	0	0	0	0	0	0	+1 NCS	0
			Month 2	22JAN2014(51)	0	0	0	0	0	0	0	0
			Month 6	30MAY2014(179)	0	0	0	0	0	0	0	0
Cohort 1	1068-001	M	Baseline	02MAR2014(-3)	0	0	0	0	0	0	0	0
			Day 1	06MAR2014(1)	0	0	0	0	0	0	0	0
			Day 16	21MAR2014(16)	0	0	0	0	0	0	0	0
			Day 21	26MAR2014(21)	0	0	0	0	0	0	0	0
			Month 2	22APR2014(48)	ND	0	0	0	0	0	0	0
			Month 6	26AUG2014(174)	ND	0	0	0	0	0	0	0
				24FEB2016(721)		0	0	0	0	0	0	
Cohort 2	3064-001	M	Baseline	07MAY2014(-2)	0	0	0	0	0	ND	0	0
			Day 1	10MAY2014(1)	0	0	0	0	ND	0	0	ND
			Day 16	25MAY2014(16)	+1 NCS	0	+1 NCS	0	0	0	0	0
			Day 21	30MAY2014(21)	0	0	0	0	0	0	0	0
			Month 2	30JUN2014(52)	0	0	0	0	0	0	0	0
			Month 6	03NOV2014(178)	0	0	0	0	0	0	0	0
Cohort 2	3005-001	M	Baseline	31JUL2014(-4)	0	0	0	0	0	0	0	0
			Day 1	05AUG2014(1)	0	0	0	0	0	0	0	0
			Day 16	20AUG2014(16)	0	0	0	0	0	0	0	+1 NCS
			Day 21	25AUG2014(21)	0	0	0	0	0	0	+1 NCS	+1 NCS
			Month 2	08SEP2014(35)	0	0	0	0	0	0	0	+1 NCS

0=Absent, +1=Trace, +2=Positive, +3:+4=Strong Positive, ND=Not Done, CS=Clinically Significant, NCS=Not Clinically Significant

Listing 16.2.8.3 Laboratory Results: Urinalysis
Part 1 of 2

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Urinalysis							
					Protein	Glucose	Ketones	Nitrite	Bilirubin	Blood	Leukocytes	Urobilinogen
Cohort 2	3005-001	M	Month 6	12JAN2015(161)	0	0	0	+2 NCS	0	+1 NCS	0	+3:+4 NCS
Cohort 2	3063-002	F	Baseline	29OCT2014(-4)	0	0	0	0	0	0	0	0
			Day 1	03NOV2014(1)	0	0	0	0	0	0	0	0
			Day 16	18NOV2014(16)	0	0	0	0	0	0	0	0
			Day 21	23NOV2014(21)	0	0	0	0	0	0	0	0
			Month 2	18DEC2014(46)	0	0	0	0	0	0	0	0
			Month 6	21APR2015(170)	0	0	0	0	0	0	0	0
Cohort 2	3063-003	M	Baseline	24NOV2014(-2)	0	0	0	0	0	0	0	0
			Day 1	27NOV2014(1)	0	0	0	0	0	0	0	0
			Day 16	12DEC2014(16)	0	0	0	0	0	0	0	0
			Day 21	17DEC2014(21)	0	0	0	0	0	0	0	0
			Month 2	15JAN2015(50)	0	0	0	0	0	0	0	0
			Month 6	19MAY2015(174)	0	0	0	0	0	0	0	0
Cohort 2	3063-004	M	Baseline	04JAN2015(-1)	0	0	0	0	0	0	0	0
			Day 1	06JAN2015(1)	0	0	0	0	0	0	0	0
			Day 16	21JAN2015(16)	0	0	0	0	0	0	0	0
			Day 21	26JAN2015(21)	0	0	0	0	0	0	0	0
			Month 2	27FEB2015(53)	0	0	0	0	0	0	0	0
			Month 6	29JUN2015(175)	0	0	0	0	0	0	0	0
Cohort 3	1068-002	M	Baseline	25FEB2015(-2)	0	0	0	0	0	0	0	0
			Day 1	28FEB2015(1)	0	0	0	0	0	0	+1 NCS	0
			Day 16	15MAR2015(16)	0	0	0	0	0	0	0	0
			Day 21	20MAR2015(21)	0	0	0	0	0	0	0	0
			Month 2	17APR2015(49)	ND	0	0	0	0	0	0	0
			Month 6	12AUG2015(166)	ND	0	0	0	0	0	0	0
Cohort 3	3064-002	M	Baseline	07APR2015(-2)	0	0	0	0	0	0	0	0
			Day 1	10APR2015(1)	0	0	0	0	0	0	0	0
			Day 16	25APR2015(16)	0	0	0	0	0	0	0	0
			Day 21	30APR2015(21)	0	0	0	0	0	0	0	0
			Month 2	01JUN2015(53)	0	0	0	0	0	0	0	0

0=Absent, +1=Trace, +2=Positive, +3:+4=Strong Positive, ND=Not Done, CS=Clinically Significant, NCS=Not Clinically Significant

Listing 16.2.8.3 Laboratory Results: Urinalysis
Part 1 of 2

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Urinalysis							
					Protein	Glucose	Ketones	Nitrite	Bilirubin	Blood	Leukocytes	Urobilinogen
Cohort 3	3064-002	M	Month 6	28SEP2015(172)	0	0	0	0	0	0	0	0

0=Absent, +1=Trace, +2=Positive, +3:+4=Strong Positive, ND=Not Done, CS=Clinically Significant, NCS=Not Clinically Significant

Listing 16.2.8.3 Urinalysis Results

Part 2 of 2

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Specific Gravity	pH	Microscopy						
							WBC	RBC	Epithelial Cells	Bacteria	Casts	Crystals	Mucus
Cohort 1	3063-001	M	Baseline	17SEP2013(-1)	1.015	7.0	+1 NCS	0	0	0	0	0	0
			Day 1	19SEP2013(1)	1.010	7.0	0	0	+1 NCS	+1 NCS	0	0	0
			Day 16	04OCT2013(16)	1.010	5.0	0	0	0	0	0	0	0
			Day 21	09OCT2013(21)	1.010	7.0	0	0	0	0	0	0	0
			Month 2	19NOV2013(62)	1.010	8.0	0	0	0	0	0	0	0
			Month 6	24MAR2014(187)	1.020	5.0	0	0	0	0	0	0	0
				21SEP2015(733)	1.005	7.0	0	0	0	0	0	0	0
Cohort 1	1012-001	M	Baseline	27NOV2013(-5)	1.004	7.0	0	0	0	0	0	0	+1 NCS
			Day 1	03DEC2013(1)	1.005	6.0	0	0	ND	ND	ND	ND	ND
			Day 16	18DEC2013(16)	1.002	8.0	0	0	0	0	0	0	0
			Day 21	23DEC2013(21)	1.005	7.0	0	0	0	0	0	0	+1 NCS
			Month 2	22JAN2014(51)	1.003	6.0	0	0	0	0	0	0	0
			Month 6	30MAY2014(179)	1.005	6.0	ND	ND	ND	ND	ND	ND	ND
Cohort 1	1068-001	M	Baseline	02MAR2014(-3)	1.003	7.0	0	0	0	ND	ND	ND	ND
			Day 1	06MAR2014(1)	1.004 NCS	7.0	ND	ND	ND	ND	ND	ND	ND
			Day 16	21MAR2014(16)	1.013	7.0	0	0	0	ND	ND	ND	ND
			Day 21	26MAR2014(21)	1.005 NCS	7.0	0	0	0	ND	ND	ND	ND
			Month 2	22APR2014(48)	1.007 NCS	7.0	+1	0	0	ND	ND	ND	ND
			Month 6	26AUG2014(174)	1.007 NCS	6.5	+1 NCS	0	0	ND	ND	ND	ND
				24FEB2016(721)	1.024	8.5	0	0	0	ND	ND	ND	ND
Cohort 2	3064-001	M	Baseline	07MAY2014(-2)	ND	5.0	+1 NCS	0	0	0	0	0	0
			Day 1	10MAY2014(1)	1.005	6.0	0	0	0	0	0	0	0
			Day 16	25MAY2014(16)	ND	5.0	ND	ND	ND	ND	ND	ND	ND
			Day 21	30MAY2014(21)	1.000	6.5	0	0	0	0	0	0	0
			Month 2	30JUN2014(52)	1.010	ND	0	0	0	0	0	0	0
			Month 6	03NOV2014(178)	1.010	6.5	0	0	0	0	+1 NCS	0	0
Cohort 2	3005-001	M	Baseline	31JUL2014(-4)	1.010	7.0	0	0	0	0	0	0	0
			Day 1	05AUG2014(1)	1.015	6.5	0	0	0	+1 NCS	0	0	0
			Day 16	20AUG2014(16)	1.010	7.0	0	0	0	+1 NCS	0	0	0
			Day 21	25AUG2014(21)	1.015	7.0	0	0	0	+1 NCS	0	0	0

0=Absent, +1=Trace, +2=Positive, +3:+4=Strong Positive, ND=Not Done, CS=Clinically Significant, NCS=Not Clinically Significant

Listing 16.2.8.3 Urinalysis Results
Part 2 of 2

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Specific Gravity	pH	Microscopy						
							WBC	RBC	Epithelial Cells	Bacteria	Casts	Crystals	Mucus
Cohort 2	3005-001	M	Month 2	08SEP2014(35)	1.015	7.0	+1 NCS	+1 NCS	ND	0	ND	ND	ND
			Month 6	12JAN2015(161)	1.020	7.0	+1 NCS	+1 NCS	ND	ND	ND	ND	ND
Cohort 2	3063-002	F	Baseline	29OCT2014(-4)	1.020	8.0	+1 NCS	0	+1 NCS	0	0	0	0
			Day 1	03NOV2014(1)	1.101	8.0	0	0	0	0	0	0	0
			Day 16	18NOV2014(16)	1.005	5.0	0	0	+1 NCS	0	0	0	0
			Day 21	23NOV2014(21)	1.020	5.0	0	0	+1 NCS	0	0	0	0
			Month 2	18DEC2014(46)	1.010	6.0	+1 NCS	0	0	0	0	0	0
			Month 6	21APR2015(170)	1.010	5.0	0	0	0	0	0	0	0
Cohort 2	3063-003	M	Baseline	24NOV2014(-2)	1.005	5.0	0	0	0	0	0	0	0
			Day 1	27NOV2014(1)	1.005	5.0	0	0	0	0	0	0	0
			Day 16	12DEC2014(16)	1.005	6.5	0	0	0	0	0	0	0
			Day 21	17DEC2014(21)	1.005	7.0	0	0	0	0	0	0	0
			Month 2	15JAN2015(50)	1.005	8.0	0	0	0	0	0	0	0
			Month 6	19MAY2015(174)	1.015	6.0	0	0	0	0	0	0	0
Cohort 2	3063-004	M	Baseline	04JAN2015(-1)	1.005	6.5	0	0	0	0	0	0	0
			Day 1	06JAN2015(1)	1.010	5.0	0	0	0	0	0	0	0
			Day 16	21JAN2015(16)	1.005	6.5	0	0	0	0	0	0	0
			Day 21	26JAN2015(21)	1.010	8.0	0	0	0	0	0	0	0
			Month 2	27FEB2015(53)	1.010	8.0	0	0	0	0	0	0	0
			Month 6	29JUN2015(175)	1.005	8.0	0	0	0	0	0	0	0
Cohort 3	1068-002	M	Baseline	25FEB2015(-2)	1.008	7.0	0	0	0	ND	ND	ND	ND
			Day 1	28FEB2015(1)	1.005 NCS	7.0	0	0	0	ND	ND	ND	ND
			Day 16	15MAR2015(16)	1.010	7.0	0	0	0	ND	ND	ND	ND
			Day 21	20MAR2015(21)	1.010	7.5	0	0	0	ND	ND	ND	ND
			Month 2	17APR2015(49)	1.029 NCS	7.5	+1	+1	0	ND	ND	ND	ND
			Month 6	12AUG2015(166)	1.009	8.0 NCS	0	0	0	ND	ND	ND	ND
Cohort 3	3064-002	M	Baseline	07APR2015(-2)	1.005	5.0	0	+1 NCS	0	0	0	0	0
			Day 1	10APR2015(1)	1.000	5.0	0	0	0	0	0	0	0
			Day 16	25APR2015(16)	1.005	6.0	0	0	0	0	0	0	0

0=Absent, +1=Trace, +2=Positive, +3:+4=Strong Positive, ND=Not Done, CS=Clinically Significant, NCS=Not Clinically Significant

Listing 16.2.8.3 Urinalysis Results
Part 2 of 2

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Specific Gravity	pH	Microscopy						
							WBC	RBC	Epithelial Cells	Bacteria	Casts	Crystals	Mucus
Cohort 3	3064-002	M	Day 21	30APR2015(21)	1.005	6.5	0	0	0	0	0	0	0
			Month 2	01JUN2015(53)	1.000	6.0	0	0	0	0	0	0	0
			Month 6	28SEP2015(172)	1.005	7.0	0	0	0	0	0	0	0

0=Absent, +1=Trace, +2=Positive, +3:+4=Strong Positive, ND=Not Done, CS=Clinically Significant, NCS=Not Clinically Significant

Listing 16.2.8.4 Laboratory Results: Out of Range Values

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Laboratory Type	Laboratory Parameter	Laboratory Value	Laboratory Unit	High/Low
Cohort 1	3063-001	M	Baseline	17SEP2013(-1)	Hematology	Hematocrit	54.8	%	H
			Baseline	17SEP2013(-1)	Hematology	Platelets	162	x10E3/uL	L
			Baseline	17SEP2013(-1)	Hematology	Neutrophils	7.1	x10E3/uL	H
			Baseline	17SEP2013(-1)	Hematology	Monocytes	0.5	x10E3/uL	L
			Day 1	19SEP2013(1)	Hematology	Hematocrit	56.6	%	H
			Day 1	19SEP2013(1)	Hematology	Platelets	165	x10E3/uL	L
			Day 1	19SEP2013(1)	Hematology	Eosinophils	0.7	x10E3/uL	H
			Unscheduled	20SEP2013(2)	Chemistry	Creatinine	0.29	mg/dL	L
			Day 16	04OCT2013(16)	Chemistry	Sodium (Na)	131	mmol/L	L
			Day 16	04OCT2013(16)	Chemistry	BUN	6	mg/dL	L
			Day 16	04OCT2013(16)	Chemistry	Glucose	100	mg/dL	H
			Day 16	04OCT2013(16)	Chemistry	Creatinine	0.23	mg/dL	L
			Day 16	04OCT2013(16)	Chemistry	Albumin	31.2	g/L	L
			Day 16	04OCT2013(16)	Hematology	Hemoglobin	15.8	g/dL	H
			Day 21	09OCT2013(21)	Chemistry	Sodium (Na)	129	mmol/L	L
			Day 21	09OCT2013(21)	Chemistry	Glucose	102	mg/dL	H
			Day 21	09OCT2013(21)	Chemistry	Creatinine	0.25	mg/dL	L
			Day 21	09OCT2013(21)	Chemistry	Albumin	30.1	g/L	L
			Month 2	20NOV2013(63)	Chemistry	Albumin	36.6	g/L	L
			Month 6	24MAR2014(187)	Chemistry	Creatinine	0.15	mg/dL	L
			Month 6	24MAR2014(187)	Hematology	RBC	5.25	x10E6/uL	H
			Month 6	24MAR2014(187)	Hematology	Hematocrit	38.1	%	H
			Month 6	24MAR2014(187)	Hematology	Monocytes	0.2	x10E3/uL	L
			Month 6	24MAR2014(187)	Hematology	Eosinophils	2.4	x10E3/uL	H
			Month 6	24MAR2014(187)	Hematology	Basophils	0	x10E3/uL	L
Cohort 1	1012-001	M	Baseline	26NOV2013(-6)	Chemistry	Calcium (Ca)	2.89	mmol/L	H
			Day 16	18DEC2013(16)	Chemistry	Creatinine	<0.30	mg/dL	L
			Day 16	18DEC2013(16)	Hematology	Hemoglobin	11.9	g/dL	L
			Day 16	18DEC2013(16)	Hematology	Hematocrit	35.0	%	L
			Day 21	23DEC2013(21)	Chemistry	Calcium (Ca)	2.74	mmol/L	H
			Month 2	22JAN2014(51)	Chemistry	Creatinine	<0.30	mg/dL	L
			Month 2	22JAN2014(51)	Hematology	Hematocrit	30.9	%	L
			Month 6	30MAY2014(179)	Chemistry	Creatinine	<0.30	mg/dL	L
			Month 6	30MAY2014(179)	Hematology	RBC	5.16	x10E6/uL	H
			Month 6	30MAY2014(179)	Hematology	Neutrophils	0.82	x10E3/uL	L

H=High, L=Low

Listing 16.2.8.4 Laboratory Results: Out of Range Values

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Laboratory Type	Laboratory Parameter	Laboratory Value	Laboratory Unit	High/Low
Cohort 1	1068-001	M	Baseline	03MAR2014(-2)	Chemistry	Sodium (Na)	134	mmol/L	L
			Baseline	03MAR2014(-2)	Chemistry	BUN	4	mg/dL	L
			Baseline	03MAR2014(-2)	Chemistry	Total Protein	48	g/L	L
			Baseline	03MAR2014(-2)	Hematology	Monocytes	1.26	x10E3/uL	H
			Day 1	06MAR2014(1)	Chemistry	BUN	3	mg/dL	L
			Day 1	06MAR2014(1)	Chemistry	Total Protein	52	g/L	L
			Day 1	06MAR2014(1)	Hematology	Platelets	495	x10E3/uL	H
			Day 1	06MAR2014(1)	Hematology	Monocytes	2.00	x10E3/uL	H
			Day 16	21MAR2014(16)	Chemistry	Potassium (K)	5.3	mmol/L	H
			Day 16	21MAR2014(16)	Chemistry	BUN	7	mg/dL	L
			Day 16	21MAR2014(16)	Chemistry	Total Protein	53	g/L	L
			Day 16	21MAR2014(16)	Hematology	Monocytes	1.80	x10E3/uL	H
			Day 21	26MAR2014(21)	Chemistry	BUN	7	mg/dL	L
			Day 21	26MAR2014(21)	Hematology	Neutrophils	2.10	x10E3/uL	L
			Day 21	26MAR2014(21)	Hematology	Monocytes	1.95	x10E3/uL	H
			Month 2	22APR2014(48)	Chemistry	Potassium (K)	5.9	mmol/L	H
			Month 2	22APR2014(48)	Chemistry	AST (SGOT)	94	U/L	H
			Month 2	22APR2014(48)	Chemistry	ALT (SGPT)	90	U/L	H
			Month 2	22APR2014(48)	Hematology	Platelets	468	x10E3/uL	H
			Month 2	22APR2014(48)	Hematology	Monocytes	1.45	x10E3/uL	H
			Month 2	23APR2014(49)	Chemistry	ALT (SGPT)	64	U/L	H
				24FEB2016(721)	Hematology	WBC	4.7	x10E3/uL	L
				24FEB2016(721)	Hematology	Hemoglobin	10.7	g/dL	L
				24FEB2016(721)	Hematology	Hematocrit	31.2	%	L
Cohort 2	3064-001	M	Baseline	09MAY2014(0)	Chemistry	Albumin	30	g/L	L
			Baseline	09MAY2014(0)	Hematology	WBC	21.1	x10E3/uL	H
			Baseline	09MAY2014(0)	Hematology	Platelets	504	x10E3/uL	H
			Baseline	09MAY2014(0)	Hematology	Monocytes	3.30	x10E3/uL	H
			Baseline	09MAY2014(0)	Hematology	Basophils	0.50	x10E3/uL	H
			Day 1	10MAY2014(1)	Chemistry	Albumin	27	g/L	L
			Day 1	10MAY2014(1)	Hematology	WBC	41.4	x10E3/uL	H
			Day 1	10MAY2014(1)	Hematology	Neutrophils	28.98	x10E3/uL	H
			Day 1	10MAY2014(1)	Hematology	Lymphocytes	10.35	x10E3/uL	H
			Day 1	10MAY2014(1)	Hematology	Monocytes	1.66	x10E3/uL	H
			Unscheduled	12MAY2014(3)	Hematology	WBC	26.0	x10E3/uL	H

H=High, L=Low

Listing 16.2.8.4 Laboratory Results: Out of Range Values

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Laboratory Type	Laboratory Parameter	Laboratory Value	Laboratory Unit	High/Low
Cohort 2	3064-001	M	Unscheduled	12MAY2014(3)	Hematology	Neutrophils	15.8	x10E3/uL	H
			Unscheduled	12MAY2014(3)	Hematology	Monocytes	3.20	x10E3/uL	H

H=High, L=Low

Listing 16.2.8.4 Laboratory Results: Out of Range Values

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Laboratory Type	Laboratory Parameter	Laboratory Value	Laboratory Unit	High/Low
Cohort 2	3064-001	M	Unscheduled	12MAY2014(3)	Hematology	Basophils	0.80	x10E3/uL	H
			Unscheduled	13MAY2014(4)	Chemistry	Calcium (Ca)	2.72	mmol/L	H
			Unscheduled	13MAY2014(4)	Chemistry	Creatinine	0.41	mg/dL	H
			Unscheduled	13MAY2014(4)	Chemistry	Albumin	26	g/L	L
			Unscheduled	13MAY2014(4)	Hematology	WBC	19.3	x10E3/uL	H
			Unscheduled	13MAY2014(4)	Hematology	Platelets	618	x10E3/uL	H
			Unscheduled	13MAY2014(4)	Hematology	Neutrophils	10.80	x10E3/uL	H
			Unscheduled	13MAY2014(4)	Hematology	Monocytes	2.60	x10E3/uL	H
			Unscheduled	13MAY2014(4)	Hematology	Basophils	0.50	x10E3/uL	H
			Unscheduled	16MAY2014(7)	Chemistry	Calcium (Ca)	2.74	mmol/L	H
			Unscheduled	16MAY2014(7)	Chemistry	Albumin	24	g/L	L
			Unscheduled	16MAY2014(7)	Hematology	Platelets	738	x10E3/uL	H
			Unscheduled	16MAY2014(7)	Hematology	Monocytes	2.60	x10E3/uL	H
			Unscheduled	16MAY2014(7)	Hematology	Basophils	0.40	x10E3/uL	H
			Unscheduled	19MAY2014(10)	Chemistry	Albumin	24	g/L	L
			Unscheduled	19MAY2014(10)	Hematology	WBC	20.8	x10E3/uL	H
			Unscheduled	19MAY2014(10)	Hematology	Platelets	797	x10E3/uL	H
			Unscheduled	19MAY2014(10)	Hematology	Monocytes	2.90	x10E3/uL	H
			Unscheduled	19MAY2014(10)	Hematology	Basophils	0.60	x10E3/uL	H
			Day 16	25MAY2014(16)	Chemistry	Albumin	25	g/L	L
			Day 16	25MAY2014(16)	Hematology	Hemoglobin	11.0	g/dL	L
			Day 16	25MAY2014(16)	Hematology	Platelets	580	x10E3/uL	H
			Day 16	25MAY2014(16)	Hematology	Monocytes	1.70	x10E3/uL	H
			Day 16	25MAY2014(16)	Hematology	Basophils	0.30	x10E3/uL	H
			Day 21	30MAY2014(21)	Chemistry	Calcium (Ca)	2.75	mmol/L	H
			Day 21	30MAY2014(21)	Chemistry	Albumin	28	g/L	L
			Day 21	30MAY2014(21)	Hematology	Hemoglobin	11.0	g/dL	L
			Day 21	30MAY2014(21)	Hematology	Platelets	533	x10E3/uL	H
			Month 2	30JUN2014(52)	Chemistry	Albumin	31	g/L	L
			Month 2	30JUN2014(52)	Hematology	Hemoglobin	10.0	g/dL	L
			Month 2	30JUN2014(52)	Hematology	Hematocrit	29	%	L
			Month 2	30JUN2014(52)	Hematology	Platelets	598	x10E3/uL	H
			Month 6	03NOV2014(178)	Chemistry	Creatinine	0.42	mg/dL	H
			Month 6	03NOV2014(178)	Hematology	Platelets	511	x10E3/uL	H
Cohort 2	3005-001	M	Baseline	31JUL2014(-4)	Chemistry	Chloride (Cl)	107	mmol/L	H

H=High, L=Low

Listing 16.2.8.4 Laboratory Results: Out of Range Values

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Laboratory Type	Laboratory Parameter	Laboratory Value	Laboratory Unit	High/Low
Cohort 2	3005-001	M	Baseline	31JUL2014(-4)	Chemistry	Albumin	35.5	g/L	L
			Baseline	31JUL2014(-4)	Hematology	Hemoglobin	9.9	g/dL	L
			Baseline	31JUL2014(-4)	Hematology	Hematocrit	28.4	%	L
			Baseline	31JUL2014(-4)	Hematology	Neutrophils	22	x10E3/uL	H
			Baseline	31JUL2014(-4)	Hematology	Lymphocytes	62	x10E3/uL	H
			Baseline	31JUL2014(-4)	Hematology	Monocytes	12	x10E3/uL	H
			Baseline	31JUL2014(-4)	Hematology	Eosinophils	3	x10E3/uL	H
			Day 1	05AUG2014(1)	Chemistry	Chloride (Cl)	108	mmol/L	H
			Day 1	05AUG2014(1)	Chemistry	Albumin	32	g/L	L
			Day 1	05AUG2014(1)	Chemistry	Alkaline Phosphatase	319	U/L	H
			Day 1	05AUG2014(1)	Hematology	RBC	2.72	x10E6/uL	L
			Day 1	05AUG2014(1)	Hematology	Hemoglobin	8.7	g/dL	L
			Day 1	05AUG2014(1)	Hematology	Hematocrit	24.9	%	L
			Day 1	05AUG2014(1)	Hematology	Neutrophils	21	x10E3/uL	H
			Day 1	05AUG2014(1)	Hematology	Lymphocytes	64	x10E3/uL	H
			Day 1	05AUG2014(1)	Hematology	Monocytes	11	x10E3/uL	H
			Day 1	05AUG2014(1)	Hematology	Eosinophils	3	x10E3/uL	H
			Day 16	20AUG2014(16)	Chemistry	Chloride (Cl)	107	mmol/L	H
			Day 16	20AUG2014(16)	Chemistry	Glucose	100.9	mg/dL	H
			Day 16	20AUG2014(16)	Chemistry	Alkaline Phosphatase	368	U/L	H
			Day 16	20AUG2014(16)	Hematology	RBC	3.04	x10E6/uL	L
			Day 16	20AUG2014(16)	Hematology	Hematocrit	27.4	%	L
			Day 16	20AUG2014(16)	Hematology	Neutrophils	18	x10E3/uL	H
			Day 16	20AUG2014(16)	Hematology	Lymphocytes	70	x10E3/uL	H
			Day 16	20AUG2014(16)	Hematology	Monocytes	10	x10E3/uL	H
			Day 16	20AUG2014(16)	Hematology	Eosinophils	2	x10E3/uL	H
			Day 21	25AUG2014(21)	Chemistry	Alkaline Phosphatase	340	U/L	H
			Day 21	25AUG2014(21)	Hematology	RBC	2.75	x10E6/uL	L
			Day 21	25AUG2014(21)	Hematology	Hemoglobin	8.1	g/dL	L
			Day 21	25AUG2014(21)	Hematology	Hematocrit	23.9	%	L
			Day 21	25AUG2014(21)	Hematology	Neutrophils	22	x10E3/uL	H
			Day 21	25AUG2014(21)	Hematology	Lymphocytes	68	x10E3/uL	H
			Day 21	25AUG2014(21)	Hematology	Monocytes	7	x10E3/uL	H
			Day 21	25AUG2014(21)	Hematology	Eosinophils	3	x10E3/uL	H
			Month 2	08SEP2014(35)	Chemistry	Chloride (Cl)	107	mmol/L	H
			Month 2	08SEP2014(35)	Chemistry	Alkaline Phosphatase	393	U/L	H

H=High, L=Low

Listing 16.2.8.4 Laboratory Results: Out of Range Values

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Laboratory Type	Laboratory Parameter	Laboratory Value	Laboratory Unit	High/Low
Cohort 2	3005-001	M	Month 2	08SEP2014(35)	Hematology	RBC	3.55	x10E6/uL	L
			Month 2	08SEP2014(35)	Hematology	Eosinophils	0.4	x10E3/uL	H
			Month 6	12JAN2015(161)	Hematology	RBC	4.9	x10E6/uL	H
			Month 6	12JAN2015(161)	Hematology	Hemoglobin	12.5	g/dL	H
			Month 6	12JAN2015(161)	Hematology	Hematocrit	36.3	%	H
			Month 6	12JAN2015(161)	Hematology	Neutrophils	22	x10E3/uL	H
			Month 6	12JAN2015(161)	Hematology	Lymphocytes	63	x10E3/uL	H
			Month 6	12JAN2015(161)	Hematology	Monocytes	9	x10E3/uL	H
			Month 6	12JAN2015(161)	Hematology	Eosinophils	6	x10E3/uL	H
Cohort 2	3063-002	F	Baseline	29OCT2014(-4)	Chemistry	Calcium (Ca)	2.7	mmol/L	H
			Baseline	29OCT2014(-4)	Chemistry	Glucose	87	mg/dL	H
			Baseline	29OCT2014(-4)	Chemistry	Albumin	35.8	g/L	L
			Baseline	29OCT2014(-4)	Hematology	RBC	4.06	x10E6/uL	L
			Baseline	29OCT2014(-4)	Hematology	Monocytes	0.4	10^3/uL	L
			Day 1	03NOV2014(1)	Chemistry	Glucose	105	mg/dL	H
			Day 1	03NOV2014(1)	Chemistry	Albumin	35.8	g/L	L
			Day 1	03NOV2014(1)	Hematology	Eosinophils	0.8	10^3/uL	H
			Unscheduled	12NOV2014(10)	Chemistry	Chloride (Cl)	109	mmol/L	H
			Unscheduled	12NOV2014(10)	Chemistry	Glucose	125	mg/dL	H
			Unscheduled	12NOV2014(10)	Chemistry	Creatinine	0.25	mg/dL	L
			Unscheduled	12NOV2014(10)	Hematology	WBC	18.73	x10E3/uL	H
			Unscheduled	12NOV2014(10)	Hematology	Platelets	621	x10E3/uL	H
			Unscheduled	12NOV2014(10)	Hematology	Neutrophils	7.8	10^3/uL	H
			Unscheduled	12NOV2014(10)	Hematology	Monocytes	2.6	10^3/uL	H
			Unscheduled	12NOV2014(10)	Hematology	Basophils	0.2	10^3/uL	H
			Unscheduled	14NOV2014(12)	Hematology	Platelets	630	x10E3/uL	H
			Day 16	18NOV2014(16)	Chemistry	Chloride (Cl)	109	mmol/L	H
			Day 16	18NOV2014(16)	Chemistry	Glucose	90	mg/dL	H
			Day 16	18NOV2014(16)	Chemistry	Creatinine	0.30	mg/dL	L
			Day 16	18NOV2014(16)	Chemistry	Albumin	34.4	g/L	L
			Day 16	18NOV2014(16)	Hematology	Monocytes	1.3	10^3/uL	H
			Day 16	18NOV2014(16)	Hematology	Basophils	0.1	10^3/uL	H
			Day 21	23NOV2014(21)	Chemistry	Creatinine	0.21	mg/dL	L
			Day 21	23NOV2014(21)	Hematology	Hemoglobin	12.1	g/dL	H
			Month 2	18DEC2014(46)	Chemistry	Creatinine	0.24	mg/dL	L

H=High, L=Low

Listing 16.2.8.4 Laboratory Results: Out of Range Values

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Laboratory Type	Laboratory Parameter	Laboratory Value	Laboratory Unit	High/Low
Cohort 2	3063-002	F	Month 2	18DEC2014(46)	Hematology	Neutrophils	1.2	10^3/uL	L
			Month 6	21APR2015(170)	Chemistry	Chloride (Cl)	111	mmol/L	H
			Month 6	21APR2015(170)	Hematology	WBC	14.61	x10E3/uL	H
			Month 6	21APR2015(170)	Hematology	Hematocrit	38.3	%	H
			Month 6	21APR2015(170)	Hematology	Lymphocytes	10.4	10^3/uL	H
			Month 6	21APR2015(170)	Hematology	Basophils	0.1	10^3/uL	H
Cohort 2	3063-003	M	Baseline	24NOV2014(-2)	Chemistry	Chloride (Cl)	109	mmol/L	H
			Baseline	24NOV2014(-2)	Chemistry	BUN	7	mg/dL	L
			Baseline	24NOV2014(-2)	Chemistry	Glucose	91	mg/dL	H
			Baseline	24NOV2014(-2)	Chemistry	Albumin	32.1	g/L	L
			Baseline	24NOV2014(-2)	Chemistry	AST (SGOT)	18	U/L	L
			Baseline	24NOV2014(-2)	Hematology	RBC	3.70	x10E6/uL	L
			Baseline	24NOV2014(-2)	Hematology	Hemoglobin	12.0	g/dL	L
			Baseline	24NOV2014(-2)	Hematology	Hematocrit	35.0	%	L
			Day 1	27NOV2014(1)	Chemistry	Chloride (Cl)	111	mmol/L	H
			Day 1	27NOV2014(1)	Chemistry	BUN	4	mg/dL	L
			Day 1	27NOV2014(1)	Chemistry	Albumin	32.9	g/L	L
			Day 1	27NOV2014(1)	Chemistry	AST (SGOT)	18	U/L	L
			Day 1	27NOV2014(1)	Hematology	WBC	17.09	x10E3/uL	H
			Day 1	27NOV2014(1)	Hematology	RBC	3.45	x10E6/uL	L
			Day 1	27NOV2014(1)	Hematology	Hemoglobin	11.3	g/dL	L
			Day 1	27NOV2014(1)	Hematology	Hematocrit	32.5	%	L
			Day 1	27NOV2014(1)	Hematology	Neutrophils	11.2	10^3/uL	H
			Day 1	27NOV2014(1)	Hematology	Monocytes	0.5	10^3/uL	L
			Day 16	12DEC2014(16)	Chemistry	Glucose	113	mg/dL	H
			Day 16	12DEC2014(16)	Chemistry	Creatinine	0.27	mg/dL	L
			Day 16	12DEC2014(16)	Chemistry	Albumin	34.3	g/L	L
			Day 16	12DEC2014(16)	Hematology	RBC	3.01	x10E6/uL	L
			Day 16	12DEC2014(16)	Hematology	Hemoglobin	9.2	g/dL	L
			Day 16	12DEC2014(16)	Hematology	Hematocrit	26.9	%	L
			Day 21	17DEC2014(21)	Chemistry	Glucose	85	mg/dL	H
			Day 21	17DEC2014(21)	Chemistry	Creatinine	0.29	mg/dL	L
			Day 21	17DEC2014(21)	Chemistry	Albumin	35.5	g/L	L
			Day 21	17DEC2014(21)	Hematology	RBC	2.93	x10E6/uL	L
			Day 21	17DEC2014(21)	Hematology	Hemoglobin	8.7	g/dL	L

H=High, L=Low

Listing 16.2.8.4 Laboratory Results: Out of Range Values

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Laboratory Type	Laboratory Parameter	Laboratory Value	Laboratory Unit	High/Low
Cohort 2	3063-003	M	Day 21	17DEC2014(21)	Hematology	Hematocrit	25.7	%	L
			Day 21	17DEC2014(21)	Hematology	Basophils	0.2	10^3/uL	H
			Month 2	15JAN2015(50)	Chemistry	Creatinine	0.22	mg/dL	L
			Month 2	15JAN2015(50)	Chemistry	Alkaline Phosphatase	541	U/L	H
			Month 2	15JAN2015(50)	Hematology	RBC	2.88	x10E6/uL	L
			Month 2	15JAN2015(50)	Hematology	Hemoglobin	8.1	g/dL	L
			Month 2	15JAN2015(50)	Hematology	Hematocrit	23.9	%	L
			Month 2	15JAN2015(50)	Hematology	Neutrophils	4.5	10^3/uL	H
			Month 2	15JAN2015(50)	Hematology	Monocytes	1.2	10^3/uL	H
			Month 2	15JAN2015(50)	Hematology	Eosinophils	0.7	10^3/uL	H
			Unscheduled	24JAN2015(59)	Chemistry	Potassium (K)	5.2	mEq/L	H
			Unscheduled	24JAN2015(59)	Chemistry	BUN	12	mg/dL	L
			Unscheduled	24JAN2015(59)	Chemistry	Glucose	118	mg/dL	H
			Unscheduled	24JAN2015(59)	Hematology	Hemoglobin	8.7	g/dL	L
			Unscheduled	24JAN2015(59)	Hematology	Hematocrit	25.1	%	L
			Unscheduled	24JAN2015(59)	Hematology	Platelets	567	x10E3/uL	H
			Unscheduled	24JAN2015(59)	Hematology	Neutrophils	9.90	10^3/uL	H
			Unscheduled	13FEB2015(79)	Hematology	Hemoglobin	8.9	g/dL	L
			Unscheduled	13FEB2015(79)	Hematology	Hematocrit	27.6	%	L
			Unscheduled	13FEB2015(79)	Hematology	Platelets	625	x10E3/uL	H
			Unscheduled	13FEB2015(79)	Hematology	Monocytes	0.85	10^3/uL	H
			Unscheduled	17MAR2015(111)	Hematology	Hemoglobin	9.5	g/dL	L
			Unscheduled	12APR2015(137)	Chemistry	BUN	6	mg/dL	L
			Unscheduled	12APR2015(137)	Chemistry	Glucose	111	mg/dL	H
			Unscheduled	12APR2015(137)	Chemistry	Total Protein	58	g/L	L
			Unscheduled	12APR2015(137)	Hematology	Hemoglobin	9.7	g/dL	L
			Unscheduled	12APR2015(137)	Hematology	Hematocrit	27.9	%	L
			Unscheduled	12APR2015(137)	Hematology	Eosinophils	0	10^3/uL	L
			Unscheduled	13APR2015(138)	Chemistry	BUN	11	mg/dL	L
			Month 6	19MAY2015(174)	Chemistry	BUN	31	mg/dL	H
			Month 6	19MAY2015(174)	Hematology	Hematocrit	29.8	%	L
Cohort 2	3063-004	M	Baseline	04JAN2015(-1)	Chemistry	Chloride (Cl)	112	mmol/L	H
			Baseline	04JAN2015(-1)	Chemistry	Glucose	85	mg/dL	H
			Baseline	04JAN2015(-1)	Hematology	WBC	7.02	x10E3/uL	L
			Baseline	04JAN2015(-1)	Hematology	Neutrophils	1.5	10^3/uL	L

H=High, L=Low

Listing 16.2.8.4 Laboratory Results: Out of Range Values

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Laboratory Type	Laboratory Parameter	Laboratory Value	Laboratory Unit	High/Low
Cohort 2	3063-004	M	Baseline	04JAN2015(-1)	Hematology	Basophils	0.2	10^3/uL	H
			Day 1	06JAN2015(1)	Chemistry	Chloride (Cl)	109	mmol/L	H
			Day 1	06JAN2015(1)	Chemistry	Albumin	34.5	g/L	L
			Day 16	21JAN2015(16)	Chemistry	Albumin	32.6	g/L	L
			Day 16	21JAN2015(16)	Hematology	Monocytes	2.8	10^3/uL	H
			Day 16	21JAN2015(16)	Hematology	Basophils	0.1	10^3/uL	H
			Day 21	26JAN2015(21)	Chemistry	Creatinine	0.29	mg/dL	L
			Day 21	26JAN2015(21)	Chemistry	Albumin	34.1	g/L	L
			Day 21	26JAN2015(21)	Hematology	Basophils	0.1	10^3/uL	H
			Month 2	27FEB2015(53)	Chemistry	Creatinine	0.24	mg/dL	L
			Month 2	27FEB2015(53)	Hematology	Monocytes	1.1	10^3/uL	H
			Month 2	27FEB2015(53)	Hematology	Eosinophils	0.70	10^3/uL	H
			Month 6	29JUN2015(175)	Hematology	RBC	4.88	x10E6/uL	H
Cohort 3	1068-002	M	Baseline	25FEB2015(-2)	Chemistry	BUN	5	mg/dL	L
			Baseline	25FEB2015(-2)	Hematology	Platelets	461	x10E3/uL	H
			Baseline	25FEB2015(-2)	Hematology	Monocytes	2.52	x10E3/uL	H
			Baseline	26FEB2015(-1)	Chemistry	Potassium (K)	5.6	mmol/L	H
			Baseline	26FEB2015(-1)	Chemistry	BUN	4	mg/dL	L
			Unscheduled	28FEB2015(1)	Chemistry	Potassium (K)	5.6	mmol/L	H
			Day 1	28FEB2015(1)	Chemistry	BUN	4	mg/dL	L
			Day 1	28FEB2015(1)	Hematology	Platelets	444	x10E3/uL	H
			Day 1	28FEB2015(1)	Hematology	Monocytes	1.34	x10E3/uL	H
			Day 16	15MAR2015(16)	Chemistry	Sodium (Na)	134	mmol/L	L
			Day 16	15MAR2015(16)	Chemistry	Total Protein	51	g/L	L
			Day 16	15MAR2015(16)	Hematology	Monocytes	1.22	x10E3/uL	H
			Day 21	20MAR2015(21)	Hematology	Monocytes	1.12	x10E3/uL	H
			Month 2	17APR2015(49)	Chemistry	Potassium (K)	5.3	mmol/L	H
			Month 2	17APR2015(49)	Hematology	Platelets	501	x10E3/uL	H
			Month 6	12AUG2015(166)	Chemistry	BUN	7	mg/dL	L
			Month 6	12AUG2015(166)	Hematology	Monocytes	0.76	x10E3/uL	H
			Month 6	12AUG2015(166)	Hematology	Eosinophils	1.33	x10E3/uL	H
Cohort 3	3064-002	M	Baseline	09APR2015(0)	Chemistry	Creatinine	0.38	mg/dL	L
			Baseline	09APR2015(0)	Chemistry	Alkaline Phosphatase	332	U/L	H
			Baseline	09APR2015(0)	Hematology	Hemoglobin	18.0	g/dL	H

H=High, L=Low

Listing 16.2.8.4 Laboratory Results: Out of Range Values

Cohort	Patient ID	Gender	Visit	Study Date (Day)	Laboratory Type	Laboratory Parameter	Laboratory Value	Laboratory Unit	High/Low
Cohort 3	3064-002	M	Baseline	09APR2015(0)	Hematology	Hematocrit	56	%	H
			Day 1	10APR2015(1)	Chemistry	Potassium (K)	5.8	mmol/L	H
			Day 1	10APR2015(1)	Chemistry	Alkaline Phosphatase	323	U/L	H
			Day 1	10APR2015(1)	Hematology	Hemoglobin	18.0	g/dL	H
			Day 1	10APR2015(1)	Hematology	Hematocrit	56	%	H
			Unscheduled	13APR2015(4)	Chemistry	Potassium (K)	5.7	mmol/L	H
			Unscheduled	13APR2015(4)	Chemistry	Alkaline Phosphatase	337	U/L	H
			Unscheduled	24APR2015(15)	Chemistry	Potassium (K)	5.4	mmol/L	H
			Unscheduled	24APR2015(15)	Hematology	Basophils	0.3	x10E3/uL	H
			Day 16	25APR2015(16)	Chemistry	Potassium (K)	5.4	mmol/L	H
			Month 2	01JUN2015(53)	Hematology	Hemoglobin	11.0	g/dL	L
			Month 2	01JUN2015(53)	Hematology	Hematocrit	32	%	L
			Month 6	28SEP2015(172)	Hematology	Hemoglobin	12.0	g/dL	H
			Month 6	28SEP2015(172)	Hematology	Monocytes	0.4	x10E3/uL	L
			Month 6	28SEP2015(172)	Hematology	Eosinophils	0.2	x10E3/uL	L

H=High, L=Low

Listing 16.2.9 Vital Signs

Cohort	Patient ID	Gender	Visit	Time Point	Date (Day)	Time	Temperature (C)	Resp Rate (bpm)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (bpm)
Cohort 1	3063-001	M	Baseline	Physical Examination	17SEP2013(-1)		37.0	43	65	48	139
			Day 0	Physical Examination	18SEP2013(0)		36.8	43	77	49	129
				Pre-dose	18SEP2013(0)	12:05	36.9	41	72	54	133
				15min Post	18SEP2013(0)	13:40	37.1	38	72	49	146
				1hr Post	18SEP2013(0)	16:50	36.8	41	74	52	145
				4hr Post	18SEP2013(0)	20:40	36.5	47	53	31	153
				8hr Post	19SEP2013(1)	00:40	37.0	43	81	51	128
				12hr Post	19SEP2013(1)	05:10	36.4	37	81	54	153
				16hr Post	19SEP2013(1)	08:30	36.8	59	66	47	114
				20hr Post	19SEP2013(1)	13:10	36.6	61	76	50	124
			Day 1	Physical Examination	19SEP2013(1)		36.8	59	66	47	114
			Day 4	Physical Examination	22SEP2013(4)		36.5	42	73	46	131
				Pre-dose	22SEP2013(4)	13:40	36.5	42	73	46	133
				15min Post	22SEP2013(4)	15:35	36.9	35	75	55	136
				1hr Post	22SEP2013(4)	18:30	36.9	41	80	49	154
				4hr Post	22SEP2013(4)	22:30	36.8	40	86	49	171
				8hr Post	23SEP2013(5)	02:30	36.8	41	77	67	145
				12hr Post	23SEP2013(5)	06:45	37.0	48	74	48	127
				16hr Post	23SEP2013(5)	10:40	36.9	32	97	62	149
				20hr Post	23SEP2013(5)	14:30	37.0	67	80	52	137
			Day 7	Physical Examination	25SEP2013(7)		37.1	44	68	46	138
				Pre-dose	25SEP2013(7)	11:55	36.9	38	59	46	132
				15min Post	25SEP2013(7)	13:35	36.8	45	66	39	155
				1hr Post	25SEP2013(7)	16:30	37.3	54	80	54	158
				4hr Post	25SEP2013(7)	20:40	36.9	44	83	56	156
				8hr Post	26SEP2013(8)	00:45	37.0	39	64	53	163
				12hr Post	26SEP2013(8)	04:45	36.5	36	68	49	146
				16hr Post	26SEP2013(8)	08:45	37.0	43	88	42	161
				20hr Post	26SEP2013(8)	12:35	36.9	43	83	46	153
			Day 11	Physical Examination	29SEP2013(11)		36.4	51	66	32	134
				Pre-dose	29SEP2013(11)	12:55	36.4	51	66	32	134
				15min Post	29SEP2013(11)	14:30	36.6	39	75	32	122
				1hr Post	29SEP2013(11)	17:45	36.7	59	82	43	150
				4hr Post	29SEP2013(11)	21:30	36.8	43	88	51	137

BPM (Resp Rate)=breaths per minute; BPM (Heart Rate)=beats per minute; ND=Not Done

Listing 16.2.9 Vital Signs

Cohort	Patient ID	Gender	Visit	Time Point	Date (Day)	Time	Temperature (C)	Resp Rate (bpm)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (bpm)
Cohort 1	3063-001	M	Day 11	8hr Post	30SEP2013(12)	01:35	37.2	47	72	35	136
				12hr Post	30SEP2013(12)	05:30	37.2	40	66	37	117
				16hr Post	30SEP2013(12)	09:30	36.9	36	73	47	150
				20hr Post	30SEP2013(12)	13:30	36.6	44	79	46	148
			Day 14	Physical Examination	02OCT2013(14)		36.7	43	73	37	148
				Pre-dose	02OCT2013(14)	12:30	36.6	47	79	41	151
				15min Post	02OCT2013(14)	14:30	36.8	43	85	40	148
				1hr Post	02OCT2013(14)	17:30	36.7	52	92	32	160
				4hr Post	02OCT2013(14)	21:30	37.0	38	86	36	132
				8hr Post	03OCT2013(15)	01:30	36.9	47	90	29	140
				12hr Post	03OCT2013(15)	05:30	37.2	36	78	40	129
				16hr Post	03OCT2013(15)	09:30	37.0	48	84	43	152
				20hr Post	03OCT2013(15)	13:30	36.3	42	79	46	146
			Day 15	Physical Examination	03OCT2013(15)		37.0	48	84	43	152
			Day 21	Physical Examination	09OCT2013(21)		37.1	44	68	40	153
			Month 2	Physical Examination	19NOV2013(62)		36.9	35	80	37	119
			Month 4	Physical Examination	16JAN2014(120)		37.1	40	86	51	128
			Month 6	Physical Examination	24MAR2014(187)		37.3	29	84	55	118
Cohort 1	1012-001	M	Baseline	Physical Examination	26NOV2013(-6)		37.0	44	86	58	140
			Day 0	Physical Examination	02DEC2013(0)		36.4	44	106	63	154
				Pre-dose	02DEC2013(0)	10:00	36.4	44	106	63	154
				15min Post	02DEC2013(0)	12:42	36.7	44	79	31	136
				1hr Post	02DEC2013(0)	15:42	36.1	44	84	45	146
				4hr Post	02DEC2013(0)	19:42	36.6	45	72	40	128
				8hr Post	02DEC2013(0)	23:42	36.5	46	91	40	147
				12hr Post	03DEC2013(1)	03:42	36.7	38	98	60	152
				16hr Post	03DEC2013(1)	07:42	36.4	42	94	43	158
				20hr Post	03DEC2013(1)	11:42	37.1	38	84	43	146
			Day 1	Physical Examination	03DEC2013(1)		37.1	38	84	43	146
			Day 4	Physical Examination	06DEC2013(4)		36.6	32	91	42	154
				Pre-dose	06DEC2013(4)	09:45	36.6	32	91	42	154
				15min Post	06DEC2013(4)	11:45	36.7	28	96	36	131
				1hr Post	06DEC2013(4)	14:45	36.4	28	90	40	155

BPM (Resp Rate)=breaths per minute; BPM (Heart Rate)=beats per minute; ND=Not Done

Listing 16.2.9 Vital Signs

Cohort	Patient ID	Gender	Visit	Time Point	Date (Day)	Time	Temperature (C)	Resp Rate (bpm)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (bpm)
Cohort 1	1012-001	M	Day 4	4hr Post	06DEC2013(4)	18:45	36.6	28	90	53	177
				8hr Post	06DEC2013(4)	22:45	36.9	50	93	56	153
				12hr Post	07DEC2013(5)	02:45	36.8	32	88	57	148
				16hr Post	07DEC2013(5)	06:45	36.4	31	109	52	127
				20hr Post	07DEC2013(5)	10:45	36.8	35	92	59	165
			Day 7	Physical Examination	09DEC2013(7)		36.9	40	87	47	164
				Pre-dose	09DEC2013(7)	09:40	36.9	40	87	47	164
				15min Post	09DEC2013(7)	11:30	36.3	50	98	71	187
				1hr Post	09DEC2013(7)	14:15	36.5	46	91	66	156
				4hr Post	09DEC2013(7)	18:25	36.3	44	119	56	167
				8hr Post	09DEC2013(7)	22:15	36.5	42	94	49	133
				12hr Post	10DEC2013(8)	02:15	36.4	52	83	35	140
				16hr Post	10DEC2013(8)	06:15	36.5	36	103	41	160
				20hr Post	10DEC2013(8)	10:15	36.9	40	103	50	150
			Day 11	Physical Examination	13DEC2013(11)		36.4	51	100	62	167
				Pre-dose	13DEC2013(11)	11:09	36.4	51	100	62	167
				15min Post	13DEC2013(11)	12:39	36.7	41	103	66	147
				1hr Post	13DEC2013(11)	15:39	36.4	40	77	56	160
				4hr Post	13DEC2013(11)	19:39	36.7	40	69	52	172
				8hr Post	13DEC2013(11)	23:39	36.8	40	124	87	186
				12hr Post	14DEC2013(12)	03:39	36.7	40	76	43	155
				16hr Post	14DEC2013(12)	07:39	36.6	41	91	79	184
				20hr Post	14DEC2013(12)	11:39	36.5	42	92	43	176
			Day 14	Physical Examination	16DEC2013(14)		36.5	46	108	36	189
				Pre-dose	16DEC2013(14)	10:00	36.5	46	108	36	189
				15min Post	16DEC2013(14)	11:30	36.7	44	105	43	155
				1hr Post	16DEC2013(14)	14:30	36.5	47	91	39	139
				4hr Post	16DEC2013(14)	18:30	36.7	43	96	52	177
				8hr Post	16DEC2013(14)	22:30	36.5	60	109	45	176
				12hr Post	17DEC2013(15)	02:30	36.9	52	123	58	184
				16hr Post	17DEC2013(15)	06:30	36.6	44	83	38	158
				20hr Post	17DEC2013(15)	10:45	36.5	48	89	42	136
			Day 15	Physical Examination	17DEC2013(15)		37.0	50	90	57	155
			Day 21	Physical Examination	23DEC2013(21)		36.6	38	81	36	137

BPM (Resp Rate)=breaths per minute; BPM (Heart Rate)=beats per minute; ND=Not Done

Listing 16.2.9 Vital Signs

Cohort	Patient ID	Gender	Visit	Time Point	Date (Day)	Time	Temperature (C)	Resp Rate (bpm)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (bpm)
Cohort 1	1012-001	M	Month 2	Physical Examination	22JAN2014(51)		36.4	24	85	48	153
			Month 4	Physical Examination	20MAR2014(108)		36.2	24	90	53	140
			Month 6	Physical Examination	30MAY2014(179)		36.4	22	116	87	129
Cohort 1	1068-001	M	Baseline	Physical Examination	02MAR2014(-3)		36.6	50	93	71	156
			Day 0	Physical Examination	05MAR2014(0)		36.9	41	106	68	156
				Pre-dose	05MAR2014(0)	08:45	36.9	41	106	68	156
				15min Post	05MAR2014(0)	11:00	36.8	49	111	89	156
				1hr Post	05MAR2014(0)	14:01	37.2	64	94	70	141
				4hr Post	05MAR2014(0)	18:02	36.7	57	100	40	137
				8hr Post	05MAR2014(0)	22:00	37.8	60	90	65	154
				12hr Post	06MAR2014(1)	02:00	37.2	40	89	42	138
				16hr Post	06MAR2014(1)	06:00	37.4	50	70	55	164
				20hr Post	06MAR2014(1)	10:00	36.9	48	100	67	168
			Day 1	Physical Examination	06MAR2014(1)		36.9	48	100	67	168
			Day 4	Physical Examination	09MAR2014(4)		36.9	42	101	63	150
				Pre-dose	09MAR2014(4)	09:00	36.9	42	101	63	150
				15min Post	09MAR2014(4)	12:50	37.2	44	107	85	160
				1hr Post	09MAR2014(4)	15:47	36.9	46	97	58	148
				4hr Post	09MAR2014(4)	19:47	37.9	36	97	45	166
				8hr Post	09MAR2014(4)	23:30	36.7	45	ND	ND	136
				12hr Post	10MAR2014(5)	04:00	36.9	46	100	59	133
				16hr Post	10MAR2014(5)	08:00	36.7	36	99	62	130
				20hr Post	10MAR2014(5)	11:45	36.6	30	97	36	148
			Day 7	Physical Examination	12MAR2014(7)		36.9	47	94	55	168
				Pre-dose	12MAR2014(7)	08:00	36.9	47	94	55	168
				15min Post	12MAR2014(7)	11:02	37.2	56	83	45	154
				1hr Post	12MAR2014(7)	14:02	36.9	36	90	54	158
				4hr Post	12MAR2014(7)	18:02	36.7	62	111	75	128
				8hr Post	12MAR2014(7)	22:02	37.3	62	77	49	140
				12hr Post	13MAR2014(8)	02:02	36.9	52	86	45	150
				16hr Post	13MAR2014(8)	06:02	37.4	50	72	49	144
				20hr Post	13MAR2014(8)	10:02	36.6	54	78	45	136
			Day 11	Physical Examination	16MAR2014(11)		37.2	48	98	57	158

BPM (Resp Rate)=breaths per minute; BPM (Heart Rate)=beats per minute; ND=Not Done

Listing 16.2.9 Vital Signs

Cohort	Patient ID	Gender	Visit	Time Point	Date (Day)	Time	Temperature (C)	Resp Rate (bpm)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (bpm)
Cohort 1	1068-001	M	Day 11	Pre-dose	16MAR2014(11)	09:45	37.2	48	98	57	158
				15min Post	16MAR2014(11)	11:45	36.9	42	94	41	156
				1hr Post	16MAR2014(11)	14:45	36.9	52	87	73	140
				4hr Post	16MAR2014(11)	18:45	36.9	40	128	57	150
				8hr Post	16MAR2014(11)	22:45	36.6	35	119	51	150
				12hr Post	17MAR2014(12)	02:45	36.6	26	92	52	122
				16hr Post	17MAR2014(12)	06:45	36.8	38	93	61	166
				20hr Post	17MAR2014(12)	10:45	37.4	32	89	53	148
			Day 14	Physical Examination	19MAR2014(14)		36.6	40	96	54	152
				Pre-dose	19MAR2014(14)	10:00	36.6	40	96	54	152
				15min Post	19MAR2014(14)	13:01	37.3	62	79	45	159
				1hr Post	19MAR2014(14)	16:01	36.9	30	90	40	140
				4hr Post	19MAR2014(14)	20:01	36.5	38	88	66	160
				8hr Post	20MAR2014(15)	00:01	36.5	28	79	33	135
				12hr Post	20MAR2014(15)	04:01	36.6	40	93	47	175
				16hr Post	20MAR2014(15)	08:01	36.9	31	87	36	138
				20hr Post	20MAR2014(15)	12:01	36.5	40	81	34	136
			Day 15	Physical Examination	20MAR2014(15)		36.5	40	81	34	136
			Day 21	Physical Examination	26MAR2014(21)		36.5	45	86	48	165
			Month 2	Physical Examination	22APR2014(48)		36.6	32	90	84	68
			Month 4	Physical Examination	24JUN2014(111)		36.5	24	104	54	126
			Month 6	Physical Examination	26AUG2014(174)		36.2	28	103	68	113
Cohort 2	3064-001	M	Baseline	Physical Examination	07MAY2014(-2)		36.6	39	85	59	120
			Day 0	Physical Examination	09MAY2014(0)		36.7	48	85	59	130
				Pre-dose	09MAY2014(0)	14:00	36.7	32	85	59	118
				15min Post	09MAY2014(0)	17:00	37.0	48	92	59	133
				1hr Post	09MAY2014(0)	20:00	37.0	42	117	64	142
				4hr Post	10MAY2014(1)	00:00	37.4	34	115	67	169
				8hr Post	10MAY2014(1)	04:00	37.6	36	101	59	152
				12hr Post	10MAY2014(1)	08:00	37.6	30	74	46	130
				16hr Post	10MAY2014(1)	12:00	37.4	39	90	62	133
				20hr Post	10MAY2014(1)	16:00	37.3	42	83	53	141
			Day 1	Physical Examination	10MAY2014(1)		37.3	42	83	53	143

BPM (Resp Rate)=breaths per minute; BPM (Heart Rate)=beats per minute; ND=Not Done

Listing 16.2.9 Vital Signs

Cohort	Patient ID	Gender	Visit	Time Point	Date (Day)	Time	Temperature (C)	Resp Rate (bpm)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (bpm)
Cohort 2	3064-001	M	Day 4	Physical Examination	13MAY2014(4)		37.0	36	106	56	142
				Pre-dose	13MAY2014(4)	12:25	37.0	36	106	56	142
				15min Post	13MAY2014(4)	15:30	37.1	37	87	32	128
				1hr Post	13MAY2014(4)	18:30	37.1	32	101	54	150
				4hr Post	13MAY2014(4)	22:30	37.6	38	99	66	142
				8hr Post	14MAY2014(5)	02:30	37.0	31	85	42	115
				12hr Post	14MAY2014(5)	06:30	37.0	35	89	44	116
				16hr Post	14MAY2014(5)	10:30	37.0	38	69	29	129
				20hr Post	14MAY2014(5)	14:30	36.7	52	82	43	126
			Day 7	Physical Examination	16MAY2014(7)		36.9	44	77	41	146
				Pre-dose	16MAY2014(7)	11:55	36.8	36	77	41	127
				15min Post	16MAY2014(7)	15:00	37.0	48	95	62	154
				1hr Post	16MAY2014(7)	18:00	37.0	32	114	86	144
				4hr Post	16MAY2014(7)	22:00	36.8	31	112	75	146
				8hr Post	17MAY2014(8)	02:00	36.5	34	81	45	115
				12hr Post	17MAY2014(8)	06:00	37.3	33	89	49	125
				16hr Post	17MAY2014(8)	10:00	37.0	33	84	39	158
				20hr Post	17MAY2014(8)	12:00	36.4	40	76	36	136
			Day 11	Physical Examination	20MAY2014(11)		36.5	44	105	64	160
				Pre-dose	20MAY2014(11)	14:20	36.5	44	105	64	160
				15min Post	20MAY2014(11)	17:20	36.6	36	102	83	146
				1hr Post	20MAY2014(11)	20:20	36.6	40	107	72	128
				4hr Post	21MAY2014(12)	00:20	36.6	40	95	51	126
				8hr Post	21MAY2014(12)	04:20	36.7	47	91	36	130
				12hr Post	21MAY2014(12)	08:20	36.9	40	86	49	129
				16hr Post	21MAY2014(12)	12:20	36.4	ND	93	63	160
				20hr Post	21MAY2014(12)	16:20	37.1	ND	86	53	132
			Day 14	Physical Examination	23MAY2014(14)		37.0	40	86	53	140
				Pre-dose	23MAY2014(14)	11:30	37.0	46	ND	ND	140
				15min Post	23MAY2014(14)	14:30	37.1	48	ND	ND	160
				1hr Post	23MAY2014(14)	17:30	37.1	52	ND	ND	160
				4hr Post	23MAY2014(14)	21:45	36.5	36	78	41	130
				8hr Post	24MAY2014(15)	01:45	37.0	43	83	54	140
				12hr Post	24MAY2014(15)	05:45	36.9	40	87	54	ND

BPM (Resp Rate)=breaths per minute; BPM (Heart Rate)=beats per minute; ND=Not Done

Listing 16.2.9 Vital Signs

Cohort	Patient ID	Gender	Visit	Time Point	Date (Day)	Time	Temperature (C)	Resp Rate (bpm)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (bpm)
Cohort 2	3064-001	M	Day 14	16hr Post	24MAY2014(15)	09:30	37.0	40	101	52	160
				20hr Post	24MAY2014(15)	13:30	36.9	41	85	72	140
			Day 15	Physical Examination	24MAY2014(15)		37.0	48	ND	ND	136
			Day 21	Physical Examination	30MAY2014(21)		36.9	33	102	68	140
			Month 2	Physical Examination	30JUN2014(52)		37.1	26	77	33	117
			Month 4	Physical Examination	01SEP2014(115)		37.0	44	97	66	108
			Month 6	Physical Examination	03NOV2014(178)		36.5	36	114	54	140
Cohort 2	3005-001	M	Baseline	Physical Examination	31JUL2014(-4)		36.9	61	75	44	100
			Day 0	Physical Examination	04AUG2014(0)		36.9	44	84	50	180
				Pre-dose	04AUG2014(0)	09:35	36.9	44	84	50	142
				15min Post	04AUG2014(0)	13:00	37.1	38	97	71	160
				1hr Post	04AUG2014(0)	16:00	36.7	31	94	67	168
				4hr Post	04AUG2014(0)	20:00	36.8	45	97	60	153
				8hr Post	04AUG2014(0)	00:00	36.4	37	88	66	171
				12hr Post	05AUG2014(1)	04:00	36.2	43	79	62	166
				16hr Post	05AUG2014(1)	08:00	36.9	38	93	77	157
				20hr Post	05AUG2014(1)	12:00	37.1	42	95	73	171
			Day 1	Physical Examination	05AUG2014(1)		37.1	42	95	73	171
			Day 4	Physical Examination	08AUG2014(4)		37.1	48	83	38	164
				Pre-dose	08AUG2014(4)	10:30	36.5	47	83	38	153
				15min Post	08AUG2014(4)	14:00	36.6	38	86	38	140
				1hr Post	08AUG2014(4)	17:00	36.6	29	88	40	154
				4hr Post	08AUG2014(4)	21:00	37.1	46	88	71	185
				8hr Post	09AUG2014(5)	01:00	36.4	36	86	56	152
				12hr Post	09AUG2014(5)	05:00	36.6	34	93	49	151
				16hr Post	ND						
				20hr Post	ND						
			Day 7	Physical Examination	11AUG2014(7)		36.7	57	94	51	175
				Pre-dose	11AUG2014(7)	10:00	36.7	57	94	51	175
				15min Post	11AUG2014(7)	13:15	36.8	40	87	43	173
				1hr Post	11AUG2014(7)	16:15	36.4	31	85	57	141
				4hr Post	11AUG2014(7)	20:15	36.6	33	80	42	141
				8hr Post	12AUG2014(8)	00:15	36.3	34	79	48	146

BPM (Resp Rate)=breaths per minute; BPM (Heart Rate)=beats per minute; ND=Not Done

Listing 16.2.9 Vital Signs

Cohort	Patient ID	Gender	Visit	Time Point	Date (Day)	Time	Temperature (C)	Resp Rate (bpm)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (bpm)
Cohort 2	3005-001	M	Day 7	12hr Post	12AUG2014(8)	04:15	36.0	27	86	51	152
				16hr Post	12AUG2014(8)	08:15	36.3	39	89	49	176
				20hr Post	12AUG2014(8)	12:15	36.9	35	89	56	156
			Day 11	Physical Examination	14AUG2014(10)		36.6	37	90	50	143
				Pre-dose	14AUG2014(10)	11:40	36.6	39	97	55	150
				15min Post	14AUG2014(10)	14:40	36.8	53	91	48	156
				1hr Post	14AUG2014(10)	17:40	36.9	36	85	47	175
				4hr Post	14AUG2014(10)	21:40	36.2	40	95	52	199
				8hr Post	15AUG2014(11)	01:40	36.4	29	94	34	171
				12hr Post	15AUG2014(11)	05:40	36.2	58	89	50	166
				16hr Post	15AUG2014(11)	09:40	36.2	29	105	51	140
				20hr Post	15AUG2014(11)	13:40	36.6	29	78	38	135
			Day 14	Physical Examination	18AUG2014(14)		37.1	38	90	46	155
				Pre-dose	18AUG2014(14)	12:00	37.1	38	90	46	155
				15min Post	18AUG2014(14)	15:28	35.8	32	86	53	159
				1hr Post	18AUG2014(14)	18:28	36.6	30	85	37	135
				4hr Post	18AUG2014(14)	22:30	36.4	37	97	46	130
				8hr Post	19AUG2014(15)	02:30	36.6	67	72	60	141
				12hr Post	19AUG2014(15)	06:30	36.4	30	78	41	122
				16hr Post	19AUG2014(15)	10:20	36.5	32	91	49	170
				20hr Post	19AUG2014(15)	14:20	36.4	34	86	59	171
			Day 15	Physical Examination	19AUG2014(15)		36.5	31	91	49	170
			Day 21	Physical Examination	25AUG2014(21)		36.7	37	91	42	162
			Month 2	Physical Examination	08SEP2014(35)		36.8	37	91	43	148
			Month 4	Physical Examination	10NOV2014(98)		ND	ND	110	60	148
			Month 6	Physical Examination	12JAN2015(161)		37.2	48	82	56	153
Cohort 2	3063-002	F	Baseline	Physical Examination	29OCT2014(-4)		36.7	58	80	57	157
			Day 0	Physical Examination	02NOV2014(0)		36.7	50	86	54	154
				Pre-dose	02NOV2014(0)	12:20	36.7	42	86	54	145
				15min Post	02NOV2014(0)	14:00	36.9	46	81	44	138
				1hr Post	02NOV2014(0)	17:00	37.0	42	86	52	139
				4hr Post	02NOV2014(0)	21:10	36.7	49	70	39	141
				8hr Post	03NOV2014(1)	01:00	36.7	36	80	43	146

BPM (Resp Rate)=breaths per minute; BPM (Heart Rate)=beats per minute; ND=Not Done

Listing 16.2.9 Vital Signs

Cohort	Patient ID	Gender	Visit	Time Point	Date (Day)	Time	Temperature (C)	Resp Rate (bpm)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (bpm)
Cohort 2	3063-002	F	Day 0	12hr Post	03NOV2014(1)	05:00	36.7	51	76	51	174
				16hr Post	03NOV2014(1)	09:00	36.6	54	92	58	150
				20hr Post	03NOV2014(1)	13:10	36.8	61	87	54	151
			Day 1	Physical Examination	03NOV2014(1)		36.8	42	87	54	139
			Day 4	Physical Examination	05NOV2014(3)		36.5	43	78	45	136
				Pre-dose	05NOV2014(3)	11:30	36.5	38	78	39	140
				15min Post	05NOV2014(3)	13:21	36.7	34	79	38	141
				1hr Post	05NOV2014(3)	16:20	36.7	45	83	45	134
				4hr Post	05NOV2014(3)	20:20	36.8	32	85	50	136
				8hr Post	06NOV2014(4)	00:20	37.1	43	91	66	145
				12hr Post	06NOV2014(4)	04:20	36.6	42	81	51	144
				16hr Post	06NOV2014(4)	08:20	37.2	43	74	56	153
				20hr Post	06NOV2014(4)	12:20	36.9	46	77	46	149
			Day 7	Physical Examination	09NOV2014(7)		36.8	38	76	38	164
				Pre-dose	09NOV2014(7)	12:40	36.8	38	76	38	164
				15min Post	09NOV2014(7)	14:15	36.7	36	84	52	141
				1hr Post	09NOV2014(7)	17:15	36.9	59	84	48	139
				4hr Post	09NOV2014(7)	21:15	37.1	50	101	55	156
				8hr Post	10NOV2014(8)	01:15	36.7	30	55	47	122
				12hr Post	10NOV2014(8)	05:15	37.0	42	90	61	173
				16hr Post	10NOV2014(8)	09:15	37.2	32	82	35	147
				20hr Post	10NOV2014(8)	13:15	36.5	48	74	40	126
			Day 11	Physical Examination	14NOV2014(12)		36.8	38	69	32	167
				Pre-dose	14NOV2014(12)	10:56	36.8	38	69	32	167
				15min Post	14NOV2014(12)	12:30	36.9	35	66	40	116
				1hr Post	14NOV2014(12)	15:25	36.6	45	71	35	133
				4hr Post	14NOV2014(12)	19:30	36.3	54	80	40	137
				8hr Post	14NOV2014(12)	23:30	36.3	44	70	34	124
				12hr Post	15NOV2014(13)	03:30	36.2	23	71	34	127
				16hr Post	15NOV2014(13)	07:30	36.9	38	68	32	125
				20hr Post	15NOV2014(13)	11:30	36.7	52	81	42	131
			Day 14	Physical Examination	16NOV2014(14)		36.9	42	86	36	144
				Pre-dose	16NOV2014(14)	12:20	36.9	42	86	36	144
				15min Post	16NOV2014(14)	14:15	36.8	39	69	30	121

BPM (Resp Rate)=breaths per minute; BPM (Heart Rate)=beats per minute; ND=Not Done

Listing 16.2.9 Vital Signs

Cohort	Patient ID	Gender	Visit	Time Point	Date (Day)	Time	Temperature (C)	Resp Rate (bpm)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (bpm)
Cohort 2	3063-002	F	Day 14	1hr Post	16NOV2014(14)	17:15	36.5	66	79	49	130
				4hr Post	16NOV2014(14)	21:15	36.9	46	74	34	142
				8hr Post	17NOV2014(15)	01:15	36.8	40	72	43	146
				12hr Post	17NOV2014(15)	05:15	36.8	35	71	31	120
				16hr Post	17NOV2014(15)	09:15	37.0	35	81	36	129
				20hr Post	17NOV2014(15)	13:15	37.0	48	89	49	132
			Day 15	Physical Examination	17NOV2014(15)		37.0	35	81	36	129
			Day 21	Physical Examination	23NOV2014(21)		36.8	40	75	31	141
			Month 2	Physical Examination	18DEC2014(46)		37.2	37	73	48	116
			Month 4	Physical Examination	23FEB2015(113)		37.1	40	106	54	160
			Month 6	Physical Examination	21APR2015(170)		36.4	45	113	67	124
Cohort 2	3063-003	M	Baseline	Physical Examination	24NOV2014(-2)		36.6	33	82	45	122
			Day 0	Physical Examination	26NOV2014(0)		36.9	25	74	41	127
				Pre-dose	26NOV2014(0)	12:50	36.9	25	74	41	127
				15min Post	26NOV2014(0)	14:25	37.3	30	68	40	114
				1hr Post	26NOV2014(0)	17:25	37.5	55	81	45	132
				4hr Post	26NOV2014(0)	21:30	37.1	44	65	37	120
				8hr Post	27NOV2014(1)	01:25	36.7	40	67	32	111
				12hr Post	27NOV2014(1)	05:25	36.7	52	62	39	117
				16hr Post	27NOV2014(1)	09:30	36.8	44	76	36	119
				20hr Post	27NOV2014(1)	13:35	36.4	32	70	37	154
			Day 1	Physical Examination	27NOV2014(1)		36.8	41	76	36	144
			Day 4	Physical Examination	01DEC2014(5)		36.7	46	75	48	151
				Pre-dose	01DEC2014(5)	10:25	36.5	40	75	48	139
				15min Post	01DEC2014(5)	12:00	37.0	38	80	47	146
				1hr Post	01DEC2014(5)	15:00	37.1	32	100	51	150
				4hr Post	01DEC2014(5)	19:00	36.5	30	63	26	119
				8hr Post	01DEC2014(5)	23:00	36.8	48	71	30	135
				12hr Post	02DEC2014(6)	03:00	37.0	29	73	36	112
				16hr Post	02DEC2014(6)	07:00	37.3	46	70	40	130
				20hr Post	02DEC2014(6)	11:00	37.2	37	56	20	111
			Day 7	Physical Examination	04DEC2014(8)		37.0	50	66	34	142
				Pre-dose	04DEC2014(8)	10:50	37.0	50	66	34	142

BPM (Resp Rate)=breaths per minute; BPM (Heart Rate)=beats per minute; ND=Not Done

Listing 16.2.9 Vital Signs

Cohort	Patient ID	Gender	Visit	Time Point	Date (Day)	Time	Temperature (C)	Resp Rate (bpm)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (bpm)
Cohort 2	3063-003	M	Day 7	15min Post	04DEC2014(8)	13:20	36.9	38	57	38	119
				1hr Post	04DEC2014(8)	16:20	36.6	36	66	32	131
				4hr Post	04DEC2014(8)	20:20	36.6	47	71	54	127
				8hr Post	05DEC2014(9)	00:20	36.6	39	66	28	136
				12hr Post	05DEC2014(9)	04:20	37.0	42	93	59	164
				16hr Post	05DEC2014(9)	08:20	37.2	45	73	39	147
				20hr Post	05DEC2014(9)	12:20	36.9	34	62	30	114
			Day 11	Physical Examination	07DEC2014(11)		37.2	41	90	54	162
				Pre-dose	07DEC2014(11)	12:20	37.2	41	90	54	162
				15min Post	07DEC2014(11)	13:50	37.0	40	67	32	131
				1hr Post	07DEC2014(11)	16:55	37.0	30	69	28	120
				4hr Post	07DEC2014(11)	20:50	36.4	54	70	29	121
				8hr Post	08DEC2014(12)	00:50	37.0	35	65	25	129
				12hr Post	08DEC2014(12)	04:50	36.9	32	62	26	110
				16hr Post	08DEC2014(12)	08:50	36.9	57	62	26	132
				20hr Post	08DEC2014(12)	12:50	36.8	40	82	58	135
			Day 14	Physical Examination	10DEC2014(14)		37.2	44	84	47	150
				Pre-dose	10DEC2014(14)	11:30	37.2	44	84	47	150
				15min Post	10DEC2014(14)	13:15	37.0	41	83	44	133
				1hr Post	10DEC2014(14)	16:15	37.8	53	86	48	183
				4hr Post	10DEC2014(14)	20:15	36.9	55	85	48	140
				8hr Post	11DEC2014(15)	00:15	37.0	51	85	61	161
				12hr Post	11DEC2014(15)	04:15	36.9	40	94	54	155
				16hr Post	11DEC2014(15)	08:20	37.2	46	78	30	138
				20hr Post	11DEC2014(15)	12:20	37.2	45	77	47	161
			Day 15	Physical Examination	11DEC2014(15)		37.2	55	78	30	129
			Day 21	Physical Examination	17DEC2014(21)		36.9	40	75	41	122
			Month 2	Physical Examination	15JAN2015(50)		37.4	48	83	33	114
			Month 4	Physical Examination	17MAR2015(111)		37.0	40	92	43	99
			Month 6	Physical Examination	19MAY2015(174)		37.4	32	96	55	117
Cohort 2	3063-004	M	Baseline	Physical Examination	02JAN2015(-3)		36.9	45	64	47	122
			Day 0	Physical Examination	05JAN2015(0)		37.0	32	49	27	114
				Pre-dose	05JAN2015(0)	14:05	37.0	32	49	27	114

BPM (Resp Rate)=breaths per minute; BPM (Heart Rate)=beats per minute; ND=Not Done

Listing 16.2.9 Vital Signs

Cohort	Patient ID	Gender	Visit	Time Point	Date (Day)	Time	Temperature (C)	Resp Rate (bpm)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (bpm)
Cohort 2	3063-004	M	Day 0	15min Post	05JAN2015(0)	15:50	36.2	55	65	44	163
				1hr Post	05JAN2015(0)	18:50	36.5	38	51	33	127
				4hr Post	05JAN2015(0)	22:50	36.6	29	68	40	154
				8hr Post	06JAN2015(1)	02:55	37.4	34	71	56	162
				12hr Post	06JAN2015(1)	06:50	37.4	34	51	29	152
				16hr Post	06JAN2015(1)	10:50	36.7	51	52	27	138
				20hr Post	06JAN2015(1)	14:50	36.8	24	69	45	134
			Day 1	Physical Examination	06JAN2015(1)		36.7	24	62	45	121
			Day 4	Physical Examination	08JAN2015(3)		36.9	36	62	46	146
				Pre-dose	08JAN2015(3)	12:15	36.9	36	62	46	146
				15min Post	08JAN2015(3)	14:51	37.0	31	60	44	143
				1hr Post	08JAN2015(3)	17:50	37.0	32	66	45	138
				4hr Post	08JAN2015(3)	21:50	37.0	37	54	32	150
				8hr Post	09JAN2015(4)	01:50	36.9	27	63	33	130
				12hr Post	09JAN2015(4)	05:50	37.2	41	60	33	164
				16hr Post	09JAN2015(4)	09:50	36.7	46	65	38	135
				20hr Post	09JAN2015(4)	13:50	37.2	23	65	35	133
			Day 7	Physical Examination	12JAN2015(7)		37.2	37	70	34	152
				Pre-dose	12JAN2015(7)	11:10	37.2	37	70	34	152
				15min Post	12JAN2015(7)	13:20	37.3	40	62	36	138
				1hr Post	12JAN2015(7)	16:15	37.0	35	59	28	140
				4hr Post	12JAN2015(7)	20:20	37.2	43	83	37	144
				8hr Post	13JAN2015(8)	00:15	36.7	30	65	35	125
				12hr Post	13JAN2015(8)	04:20	36.7	35	69	39	142
				16hr Post	13JAN2015(8)	08:20	36.8	31	73	47	138
				20hr Post	13JAN2015(8)	12:20	36.7	53	67	34	150
			Day 11	Physical Examination	15JAN2015(10)		37.2	42	67	43	158
				Pre-dose	15JAN2015(10)	11:40	37.2	56	67	43	158
				15min Post	15JAN2015(10)	13:15	37.3	54	69	40	153
				1hr Post	15JAN2015(10)	16:15	37.5	32	63	36	161
				4hr Post	15JAN2015(10)	20:15	37.6	38	82	57	161
				8hr Post	16JAN2015(11)	00:15	37.3	42	58	31	153
				12hr Post	16JAN2015(11)	04:15	36.8	32	78	38	140
				16hr Post	16JAN2015(11)	08:15	36.9	51	64	34	154

BPM (Resp Rate)=breaths per minute; BPM (Heart Rate)=beats per minute; ND=Not Done

Listing 16.2.9 Vital Signs

Cohort	Patient ID	Gender	Visit	Time Point	Date (Day)	Time	Temperature (C)	Resp Rate (bpm)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (bpm)
Cohort 2	3063-004	M	Day 11	20hr Post	16JAN2015(11)	12:15	37.1	53	65	37	155
			Day 14	Physical Examination	19JAN2015(14)		37.6	34	77	43	160
				Pre-dose	19JAN2015(14)	11:25	37.6	34	77	43	160
				15min Post	19JAN2015(14)	13:30	37.1	32	69	36	149
				1hr Post	19JAN2015(14)	16:30	37.1	39	69	37	146
				4hr Post	19JAN2015(14)	20:30	37.1	43	68	40	162
				8hr Post	20JAN2015(15)	00:30	36.4	29	69	35	149
				12hr Post	20JAN2015(15)	04:30	37.6	40	91	49	186
				16hr Post	20JAN2015(15)	08:30	37.1	30	76	30	147
				20hr Post	20JAN2015(15)	12:30	36.6	29	68	36	140
			Day 15	Physical Examination	20JAN2015(15)		37.1	30	76	30	147
			Day 21	Physical Examination	26JAN2015(21)		37.0	52	78	44	146
			Month 2	Physical Examination	27FEB2015(53)		37.2	48	90	47	153
			Month 4	Physical Examination	30APR2015(115)		37.8	50	105	57	137
			Month 6	Physical Examination	29JUN2015(175)		37.4	36	103	48	140
Cohort 3	1068-002	M	Baseline	Physical Examination	25FEB2015(-2)		36.2	44	98	76	156
			Day 0	Physical Examination	27FEB2015(0)		36.9	40	97	55	148
				Pre-dose	27FEB2015(0)	07:00	36.9	40	97	55	148
				15min Post	27FEB2015(0)	09:15	36.9	60	87	56	152
				1hr Post	27FEB2015(0)	12:15	36.4	32	96	61	136
				4hr Post	27FEB2015(0)	16:15	36.6	43	94	58	160
				8hr Post	27FEB2015(0)	20:15	36.6	37	91	52	164
				12hr Post	28FEB2015(1)	00:15	36.8	39	81	54	150
				16hr Post	28FEB2015(1)	04:15	36.7	40	84	54	170
				20hr Post	28FEB2015(1)	08:15	36.9	58	93	56	165
				24hr Post	27FEB2015(0)	08:30	36.9	42	98	55	142
			Day 1	Physical Examination	28FEB2015(1)		36.9	58	93	56	165
			Day 4	Physical Examination	03MAR2015(4)		36.6	52	108	68	132
				Pre-dose	03MAR2015(4)	13:01	36.6	52	108	68	132
				15min Post	03MAR2015(4)	15:10	37.0	38	88	54	128
				1hr Post	03MAR2015(4)	18:10	36.6	48	108	81	156
				4hr Post	03MAR2015(4)	22:10	36.7	49	83	46	172
				8hr Post	04MAR2015(5)	02:10	36.9	40	77	38	152

BPM (Resp Rate)=breaths per minute; BPM (Heart Rate)=beats per minute; ND=Not Done

Listing 16.2.9 Vital Signs

Cohort	Patient ID	Gender	Visit	Time Point	Date (Day)	Time	Temperature (C)	Resp Rate (bpm)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (bpm)
Cohort 3	1068-002	M	Day 4	12hr Post	04MAR2015(5)	06:10	37.9	46	75	51	156
				16hr Post	04MAR2015(5)	10:10	36.6	44	93	78	142
				20hr Post	04MAR2015(5)	14:10	37.0	39	112	91	142
				24hr Post	03MAR2015(4)	14:25	36.5	42	88	72	148
			Day 7	Physical Examination	06MAR2015(7)		36.9	52	92	53	162
				Pre-dose	06MAR2015(7)	10:35	36.9	52	92	53	162
				15min Post	06MAR2015(7)	14:35	36.5	48	100	56	136
				1hr Post	06MAR2015(7)	17:35	36.1	48	81	68	130
				4hr Post	06MAR2015(7)	21:35	36.7	35	106	91	170
				8hr Post	07MAR2015(8)	01:35	36.9	44	101	51	144
				12hr Post	07MAR2015(8)	05:35	37.1	48	92	45	134
				16hr Post	07MAR2015(8)	09:35	36.5	46	90	35	144
				20hr Post	07MAR2015(8)	13:35	36.6	30	98	76	126
				24hr Post	06MAR2015(7)	13:50	36.4	38	105	88	168
			Day 11	Physical Examination	10MAR2015(11)		37.5	50	80	45	163
				Pre-dose	10MAR2015(11)	12:40	37.5	50	80	45	163
				15min Post	10MAR2015(11)	14:58	36.4	32	86	42	126
				1hr Post	10MAR2015(11)	17:58	37.1	39	91	53	146
				4hr Post	10MAR2015(11)	21:58	36.6	28	111	65	136
				8hr Post	11MAR2015(12)	01:58	37.0	32	102	55	132
				12hr Post	11MAR2015(12)	05:58	37.0	46	94	43	148
				16hr Post	11MAR2015(12)	09:58	36.7	46	78	64	148
				20hr Post	11MAR2015(12)	13:58	36.5	44	108	76	144
				24hr Post	10MAR2015(11)	14:13	36.9	42	99	80	168
			Day 14	Physical Examination	13MAR2015(14)		36.6	48	115	52	148
				Pre-dose	13MAR2015(14)	11:02	36.6	48	115	52	148
				15min Post	13MAR2015(14)	13:04	37.6	52	96	88	186
				1hr Post	13MAR2015(14)	16:04	36.8	29	94	66	139
				4hr Post	13MAR2015(14)	20:04	36.1	34	116	69	135
				8hr Post	14MAR2015(15)	00:04	36.7	37	101	48	147
				12hr Post	14MAR2015(15)	04:04	36.9	57	72	55	160
				16hr Post	14MAR2015(15)	08:04	37.0	56	74	53	160
				20hr Post	14MAR2015(15)	12:04	37.0	30	91	57	136
				24hr Post	13MAR2015(14)	12:19	36.4	40	79	65	148

BPM (Resp Rate)=breaths per minute; BPM (Heart Rate)=beats per minute; ND=Not Done

Listing 16.2.9 Vital Signs

Cohort	Patient ID	Gender	Visit	Time Point	Date (Day)	Time	Temperature (C)	Resp Rate (bpm)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (bpm)
Cohort 3	1068-002	M	Day 15	Physical Examination	14MAR2015(15)		37.0	56	74	53	160
			Day 21	Physical Examination	20MAR2015(21)		36.8	52	89	53	165
			Month 2	Physical Examination	17APR2015(49)		35.9	54	99	74	145
			Month 4	Physical Examination	19JUN2015(112)		36.3	36	101	61	87
			Month 6	Physical Examination	12AUG2015(166)		36.2	28	92	59	120
Cohort 3	3064-002	M	Baseline	Physical Examination	06APR2015(-3)		36.0	50	83	49	165
			Day 0	Physical Examination	09APR2015(0)		36.9	30	58	33	140
				Pre-dose	09APR2015(0)	11:45	36.9	30	59	33	140
				15min Post	09APR2015(0)	15:30	36.9	34	79	33	170
				1hr Post	09APR2015(0)	18:30	36.5	35	89	36	160
				4hr Post	09APR2015(0)	22:30	36.4	44	80	54	155
				8hr Post	10APR2015(1)	02:30	ND	ND	ND	ND	ND
				12hr Post	10APR2015(1)	06:30	36.9	32	69	51	162
				16hr Post	10APR2015(1)	10:30	37.1	40	89	58	167
				20hr Post	10APR2015(1)	13:45	36.5	41	100	39	160
				24hr Post	09APR2015(0)	14:45	36.4	36	ND	ND	140
			Day 1	Physical Examination	10APR2015(1)		36.4	40	72	30	155
			Day 4	Physical Examination	13APR2015(4)		36.5	58	65	32	160
				Pre-dose	13APR2015(4)	11:00	36.5	58	65	32	160
				15min Post	13APR2015(4)	14:40	36.4	34	80	30	124
				1hr Post	13APR2015(4)	16:30	36.6	38	88	52	135
				4hr Post	13APR2015(4)	21:15	37.1	38	82	50	142
				8hr Post	14APR2015(5)	01:10	36.6	38	93	48	120
				12hr Post	14APR2015(5)	05:10	36.3	37	81	48	140
				16hr Post	14APR2015(5)	09:10	36.8	48	79	53	164
				20hr Post	14APR2015(5)	13:10	36.7	42	98	61	169
				24hr Post	13APR2015(4)	13:25	36.5	36	76	41	145
			Day 7	Physical Examination	16APR2015(7)		36.0	54	66	28	161
				Pre-dose	16APR2015(7)	12:45	36.0	54	66	28	161
				15min Post	16APR2015(7)	16:00	36.8	58	73	50	170
				1hr Post	16APR2015(7)	19:05	36.0	56	104	57	155
				4hr Post	16APR2015(7)	23:15	36.4	52	80	40	164
				8hr Post	17APR2015(8)	03:00	36.0	28	61	28	142

BPM (Resp Rate)=breaths per minute; BPM (Heart Rate)=beats per minute; ND=Not Done

Listing 16.2.9 Vital Signs

Cohort	Patient ID	Gender	Visit	Time Point	Date (Day)	Time	Temperature (C)	Resp Rate (bpm)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (bpm)
Cohort 3	3064-002	M	Day 7	12hr Post	17APR2015(8)	07:00	36.2	44	75	34	164
				16hr Post	17APR2015(8)	12:00	37.2	31	79	44	142
				20hr Post	17APR2015(8)	15:15	37.0	49	89	57	158
				24hr Post	16APR2015(7)	15:15	36.8	54	67	43	170
			Day 11	Physical Examination	20APR2015(11)		36.6	39	73	29	141
				Pre-dose	20APR2015(11)	12:45	36.6	39	73	29	141
				15min Post	20APR2015(11)	17:27	36.6	38	71	41	145
				1hr Post	20APR2015(11)	22:30	36.4	28	103	48	124
				4hr Post	21APR2015(12)	02:30	36.4	36	101	52	164
				8hr Post	21APR2015(12)	05:00	36.7	41	93	58	180
				12hr Post	21APR2015(12)	08:00	36.7	24	ND	ND	145
				16hr Post	21APR2015(12)	12:30	37.2	28	ND	ND	155
				20hr Post	21APR2015(12)	16:30	36.4	36	92	46	138
				24hr Post	20APR2015(11)	16:57	36.3	40	89	54	152
			Day 14	Physical Examination	23APR2015(14)		36.8	40	100	60	162
				Pre-dose	23APR2015(14)	11:30	36.8	40	100	60	162
				15min Post	23APR2015(14)	15:30	36.0	40	81	56	160
				1hr Post	23APR2015(14)	18:30	36.0	ND	115	70	160
				4hr Post	23APR2015(14)	22:30	36.7	44	111	75	138
				8hr Post	24APR2015(15)	02:30	37.1	52	102	57	172
				12hr Post	24APR2015(15)	06:30	36.8	48	84	49	145
				16hr Post	24APR2015(15)	10:30	36.2	43	127	79	132
				20hr Post	24APR2015(15)	14:30	36.3	44	85	45	138
				24hr Post	23APR2015(14)	14:43	36.2	36	ND	ND	158
			Day 15	Physical Examination	24APR2015(15)		36.0	48	84	49	142
			Day 21	Physical Examination	30APR2015(21)		36.0	35	76	47	162
			Month 2	Physical Examination	01JUN2015(53)		36.4	64	58	29	175
			Month 4	Physical Examination	03AUG2015(116)		36.7	40	62	46	132
			Month 6	Physical Examination	28SEP2015(172)		36.3	26	102	62	101
Siblings	1068-201	M	Enrollment	Physical Examination	22APR2014		36.3	28	93	59	60
	3063-201	M	Enrollment	Physical Examination	29OCT2014		37.1	25	101	56	98

BPM (Resp Rate)=breaths per minute; BPM (Heart Rate)=beats per minute; ND=Not Done

Listing 16.2.9 Vital Signs

Cohort	Patient ID	Gender	Visit	Time Point	Date (Day)	Time	Temperature (C)	Resp Rate (bpm)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (bpm)
Siblings	3063-202	M	Enrollment	Physical Examination	25NOV2014		37.4	28	91	53	112
	3064-201	M	Enrollment	Physical Examination	01SEP2014		36.5	30	97	49	102

BPM (Resp Rate)=breaths per minute; BPM (Heart Rate)=beats per minute; ND=Not Done

Listing 16.2.10 Thermoregulation Vital Signs

Cohort	Patient ID	Visit	Time Point	Date (Day)	Time	Humidity (%)	Incubator Temperature (C)	Subject Temperature (C)	Resp Rate (breaths/min)	Pulse (beats/min)
Cohort 1	3063-001	Baseline	Start	17SEP2013(-1)	09:00	50	33.0	37.0	37	127
			30min Post	17SEP2013(-1)	09:30	50	34.0	37.3	59	116
			Removed	17SEP2013(-1)	09:55	50	34.0	37.9	56	187
			1hr Cool Down	17SEP2013(-1)	10:55	ND	ND	37.2	74	115
			2hr Cool Down	17SEP2013(-1)	11:55	ND	ND	37.2	39	136
			Return to baseline	17SEP2013(-1)	12:49	ND	ND	37.0	48	124
			3hr Cool Down	17SEP2013(-1)	12:55	ND	ND	37.0	42	143
		Day 21	Start	09OCT2013(21)	08:20	50	33.0	37.1	44	153
			30min Post	09OCT2013(21)	08:50	50	34.0	37.4	60	145
			1hr Post	09OCT2013(21)	09:20	50	35.0	37.7	71	173
			Removed	09OCT2013(21)	09:28	50	35.0	37.9	79	198
			1hr Cool Down	09OCT2013(21)	10:28	ND	ND	37.2	46	127
			Return to baseline	09OCT2013(21)	11:30	ND	ND	36.9	51	162
			3hr Cool Down	09OCT2013(21)	12:30	ND	ND	36.5	48	154
Cohort 1	1012-001	Baseline	Start	27NOV2013(-5)	12:34	25	33.0	37.0	44	140
			30min Post	27NOV2013(-5)	13:04	25	34.5	36.0	40	144
			1hr Post	27NOV2013(-5)	13:34	25	35.0	36.6	36	159
			Removed	27NOV2013(-5)	13:48	25	35.0	36.9	28	194
			1hr Cool Down	27NOV2013(-5)	13:52	ND	ND	37.0	50	185
			2hr Cool Down	27NOV2013(-5)	13:55	ND	ND	36.5	44	158
			3hr Cool Down	27NOV2013(-5)	14:00	ND	ND	35.9	41	140
			Return to baseline	27NOV2013(-5)	14:02	25	ND	36.1	40	145
		Day 21	Start	23DEC2013(21)	11:15	25	33.0	36.5	40	130
			30min Post	23DEC2013(21)	11:45	25	33.0	35.7	39	140
			1hr Post	23DEC2013(21)	12:15	25	34.0	36.6	33	178
			Removed	23DEC2013(21)	12:28	25	34.0	37.0	36	220
			1hr Cool Down	23DEC2013(21)	13:15	25	ND	36.9	36	168
			Return to baseline	23DEC2013(21)	13:30	25	ND	36.6	32	160
Cohort 1	1068-001	Baseline	Start	03MAR2014(-2)	09:00	50	33	36.4	52	166
			30min Post	03MAR2014(-2)	09:30	51	34.5	36.3	51	150
			1hr Post	03MAR2014(-2)	10:00	54	35.5	36.7	54	150
			1hr, 30min Post	03MAR2014(-2)	10:30	52	36.5	37.3	59	160
			Removed	03MAR2014(-2)	10:57	53	36.5	38.0	86	167

ND=Not Done; If the date is listed as ND, then the sort procedure will place the time point at the top of the list.

Listing 16.2.10 Thermoregulation Vital Signs

Cohort	Patient ID	Visit	Time Point	Date (Day)	Time	Humidity (%)	Incubator Temperature (C)	Subject Temperature (C)	Resp Rate (breaths/min)	Pulse (beats/min)
Cohort 1	1068-001	Baseline	Return to baseline	03MAR2014(-2)	11:17	ND	ND	36.9	42	140
			1hr Cool Down	03MAR2014(-2)	11:57	ND	ND	36.0	44	138
			2hr Cool Down	03MAR2014(-2)	12:57	ND	ND	36.8	42	130
			3hr Cool Down	03MAR2014(-2)	13:57	ND	ND	36.9	52	131
		Day 21	Start	26MAR2014(21)	08:04	50	33	36.4	55	165
			30min Post	26MAR2014(21)	08:34	52	34.5	36.6	58	172
			1hr Post	26MAR2014(21)	09:04	53	35.5	37.6	67	173
			Removed	26MAR2014(21)	09:18	50	34.8	38.0	74	202
			Return to baseline	26MAR2014(21)	09:45	ND	ND	36.9	38	152
			1hr Cool Down	26MAR2014(21)	10:18	ND	ND	36.9	38	152
			2hr Cool Down	26MAR2014(21)	11:18	ND	ND	37.2	42	139
			3hr Cool Down	26MAR2014(21)	12:18	ND	ND	36.9	32	128
Cohort 2	3064-001	Baseline	Return to baseline	ND	ND	ND	ND	ND	ND	ND
			Start	08MAY2014(-1)	07:13	50	32.8	36.7	32	131
			30min Post	08MAY2014(-1)	07:43	50	33.0	36.7	44	130
			1hr Post	08MAY2014(-1)	08:13	50	34.5	36.8	40	136
			1hr, 30min Post	08MAY2014(-1)	08:43	50	36.1	37.5	47	178
			2hr Post	08MAY2014(-1)	09:13	50	36.2	38.5	48	179
			Removed	08MAY2014(-1)	09:43	50	36.2	38.5	45	170
			1hr Cool Down	08MAY2014(-1)	10:13	ND	ND	37.2	39	144
			2hr Cool Down	08MAY2014(-1)	11:13	ND	ND	36.9	36	153
			3hr Cool Down	08MAY2014(-1)	12:13	ND	ND	37.1	33	137
		Day 21	Start	30MAY2014(21)	10:50	50	33.0	36.9	33	135
			30min Post	30MAY2014(21)	11:20	50	34.5	36.6	36	142
			1hr Post	30MAY2014(21)	11:50	50	36.0	36.7	32	145
			1hr, 30min Post	30MAY2014(21)	12:20	50	36.5	37.0	37	155
			2hr Post	30MAY2014(21)	12:50	50	36.5	37.8	47	183
			Removed	30MAY2014(21)	13:20	ND	ND	37.1	39	181
			1hr Cool Down	30MAY2014(21)	13:50	ND	ND	37.3	36	150
			2hr Cool Down	30MAY2014(21)	14:50	ND	ND	37.1	36	169
			Return to baseline	30MAY2014(21)	15:50	ND	ND	36.8	37	149
Cohort 2	3005-001	Baseline	Removed	ND	ND	ND	ND	ND	ND	ND
			Start	31JUL2014(-4)	15:00	ND	ND	36.4	47	157

ND=Not Done; If the date is listed as ND, then the sort procedure will place the time point at the top of the list.

Listing 16.2.10 Thermoregulation Vital Signs

Cohort	Patient ID	Visit	Time Point	Date (Day)	Time	Humidity (%)	Incubator Temperature (C)	Subject Temperature (C)	Resp Rate (breaths/min)	Pulse (beats/min)
Cohort 2	3005-001	Baseline	30min Post	31JUL2014(-4)	15:30	60	33.0	36.6	45	156
			1hr Post	31JUL2014(-4)	16:00	50	34.0	38.0	85	160
			1hr, 30min Post	31JUL2014(-4)	16:15	50	34.0	38.1	90	185
			1hr Cool Down	31JUL2014(-4)	17:15	ND	ND	37.2	51	165
			2hr Cool Down	31JUL2014(-4)	18:15	ND	ND	37.3	43	178
			3hr Cool Down	31JUL2014(-4)	19:15	ND	ND	37.3	56	177
		Day 21	Start	25AUG2014(21)	10:15	50	33.0	36.7	37	162
			30min Post	25AUG2014(21)	10:45	50	33.0	37.3	42	167
			1hr Post	25AUG2014(21)	11:15	50	34.0	37.6	40	186
			1hr, 30min Post	25AUG2014(21)	11:45	50	34.5	38.0	60	164
			2hr Post	25AUG2014(21)	12:15	50	35.0	38.4	70	170
			Removed	25AUG2014(21)	12:30	50	35.5	38.6	59	250
			1hr Cool Down	25AUG2014(21)	13:30	ND	ND	36.9	33	150
			2hr Cool Down	25AUG2014(21)	14:30	ND	ND	37.3	41	147
			3hr Cool Down	25AUG2014(21)	15:30	ND	ND	37.3	44	145
Cohort 2	3063-002	Baseline	Start	29OCT2014(-4)	08:43	50	33.0	36.8	43	158
			30min Post	29OCT2014(-4)	09:13	50	34.0	37.2	55	143
			1hr Post	29OCT2014(-4)	09:43	50	35.0	37.6	74	161
			Removed	29OCT2014(-4)	10:10	50	35.0	37.9	53	226
			1hr Cool Down	29OCT2014(-4)	11:10	ND	ND	37.0	41	136
			2hr Cool Down	29OCT2014(-4)	12:05	ND	ND	36.8	46	158
			Return to baseline	29OCT2014(-4)	12:05	ND	ND	36.8	46	158
			3hr Cool Down	29OCT2014(-4)	13:10	ND	ND	36.8	50	134
		Day 21	Start	23NOV2014(21)	12:25	50	33.0	36.8	40	156
			30min Post	23NOV2014(21)	12:55	50	34.0	37.1	46	139
			1hr Post	23NOV2014(21)	13:25	50	35.0	37.3	49	141
			Removed	23NOV2014(21)	13:50	50	35.0	37.5	54	201
			Return to baseline	23NOV2014(21)	14:40	ND	ND	36.8	50	155
			1hr Cool Down	23NOV2014(21)	14:50	ND	ND	36.9	53	159
			2hr Cool Down	23NOV2014(21)	15:45	ND	ND	37.1	36	136
			3hr Cool Down	23NOV2014(21)	16:45	ND	ND	37.1	44	147
Cohort 2	3063-003	Baseline	Start	24NOV2014(-2)	15:25	50	33.0	36.7	41	126
			30min Post	24NOV2014(-2)	15:55	50	34.0	37.0	26	122

ND=Not Done; If the date is listed as ND, then the sort procedure will place the time point at the top of the list.

Listing 16.2.10 Thermoregulation Vital Signs

Cohort	Patient ID	Visit	Time Point	Date (Day)	Time	Humidity (%)	Incubator Temperature (C)	Subject Temperature (C)	Resp Rate (breaths/min)	Pulse (beats/min)
Cohort 2	3063-003	Baseline	1hr Post	24NOV2014(-2)	16:25	50	35.0	37.3	34	132
			Removed	24NOV2014(-2)	16:45	50	35.0	37.9	35	172
			1hr Cool Down	24NOV2014(-2)	17:45			36.7	32	136
			Return to baseline	24NOV2014(-2)	17:45			36.7	32	136
			2hr Post	24NOV2014(-2)	18:45			37.0	35	166
			3.0 HOURS	24NOV2014(-2)	19:45			37.2	29	151
		Day 21	Start	17DEC2014(21)	09:28	50	33.0	36.9	44	141
			30min Post	17DEC2014(21)	09:58	50	34.0	37.3	46	144
			1hr Post	17DEC2014(21)	10:28	50	35.0	37.8	82	127
			Removed	17DEC2014(21)	10:36	50	35.0	37.9	87	129
			1hr Cool Down	17DEC2014(21)	11:36	ND	ND	36.9	34	125
			Return to baseline	17DEC2014(21)	11:36	ND	ND	36.9	34	125
			2hr Cool Down	17DEC2014(21)	12:35	ND	ND	36.9	29	120
			3hr Cool Down	17DEC2014(21)	13:35	ND	ND	36.8	44	119
Cohort 2	3063-004	Baseline	Start	02JAN2015(-3)	14:10	50	33.0	36.9	55	137
			30min Post	02JAN2015(-3)	14:40	50	34.0	37.2	39	127
			1hr Post	02JAN2015(-3)	15:10	50	35.0	37.8	42	169
			Removed	02JAN2015(-3)	15:13	ND	35.0	37.9	51	198
			1hr Cool Down	02JAN2015(-3)	16:15	ND	ND	37.6	49	171
			2hr Cool Down	02JAN2015(-3)	17:15	ND	ND	37.4	33	121
			3hr Cool Down	02JAN2015(-3)	18:15	ND	ND	37.3	31	128
		Day 21	Start	26JAN2015(21)	09:50	50	33.0	37.0	52	146
			30min Post	26JAN2015(21)	10:20	50	34.0	37.3	39	158
			Removed	26JAN2015(21)	10:46	50	34.0	37.9	87	207
			1hr Cool Down	26JAN2015(21)	11:46	ND	ND	37.1	44	142
			Return to baseline	26JAN2015(21)	11:54	ND	ND	37.0	35	147
			2hr Cool Down	26JAN2015(21)	12:45	ND	ND	37.0	48	140
			3hr Cool Down	26JAN2015(21)	13:45	ND	ND	36.9	42	155
Cohort 3	1068-002	Baseline	Start	25FEB2015(-2)	11:35	49	32.5	36.7	43	174
			30min Post	25FEB2015(-2)	12:05	50	32.9	36.7	44	149
			1hr Post	25FEB2015(-2)	12:35	50	34.3	36.7	36	135
			1hr, 30min Post	25FEB2015(-2)	13:05	49	35.7	37.0	45	153
			2hr Post	25FEB2015(-2)	13:35	50	36.8	37.8	49	144

ND=Not Done; If the date is listed as ND, then the sort procedure will place the time point at the top of the list.

Listing 16.2.10 Thermoregulation Vital Signs

Cohort	Patient ID	Visit	Time Point	Date (Day)	Time	Humidity (%)	Incubator Temperature (C)	Subject Temperature (C)	Resp Rate (breaths/min)	Pulse (beats/min)
Cohort 3	1068-002	Baseline	Removed	25FEB2015(-2)	13:50	50	36.5	38.0	41	209
			Return to baseline	25FEB2015(-2)	13:53	ND	ND	37.3	44	155
			1hr Cool Down	25FEB2015(-2)	14:50	ND	ND	36.9	42	148
			2hr Cool Down	25FEB2015(-2)	15:50	ND	ND	36.1	32	126
			3hr Cool Down	25FEB2015(-2)	16:50	ND	ND	36.5	47	152
		Day 21	Start	20MAR2015(21)	08:08	46	32.8	36.8	68	166
			30min Post	20MAR2015(21)	08:38	54	33.1	37.3	37	134
			1hr Post	20MAR2015(21)	09:08	52	34.5	37.7	56	144
			Removed	20MAR2015(21)	09:20	50	35.5	38.3	49	219
			Return to baseline	20MAR2015(21)	09:30	ND	ND	36.7	48	155
			1hr Cool Down	20MAR2015(21)	10:20	ND	ND	36.0	68	153
			2hr Cool Down	20MAR2015(21)	11:20	ND	ND	36.5	20	133
			3hr Cool Down	20MAR2015(21)	12:20	ND	ND	36.5	32	137
Cohort 3	3064-002	Baseline	Start	08APR2015(-1)	15:33	50	32.8	35.9	46	145
			30min Post	08APR2015(-1)	16:04	49	32.8	36.3	44	146
			1hr Post	08APR2015(-1)	16:35	50	34.0	36.6	54	165
			1hr, 30min Post	08APR2015(-1)	17:07	51	35.2	37.2	80	183
			Removed	08APR2015(-1)	17:17	50	35.5	37.3	110	223
			1hr Cool Down	08APR2015(-1)	18:17	ND	ND	36.4	48	166
			2hr Cool Down	08APR2015(-1)	19:17	ND	ND	36.2	38	137
			Return to baseline	08APR2015(-1)	19:17	ND	ND	36.2	38	137
			3hr Cool Down	08APR2015(-1)	20:17	ND	ND	36.5	48	170
		Day 21	Start	30APR2015(21)	11:15	ND	33.0	36.2	30	168
			30min Post	30APR2015(21)	11:45	ND	32.9	36.3	70	166
			1hr Post	30APR2015(21)	12:15	ND	34.0	36.7	36	202
			Removed	30APR2015(21)	12:17	ND	34.0	37.1	40	215
			1hr Cool Down	30APR2015(21)	13:17	ND	ND	36.0	36	153
			Return to baseline	30APR2015(21)	13:17	ND	ND	36.0	36	153
			2hr Cool Down	30APR2015(21)	14:17	ND	ND	36.0	30	130
			3hr Cool Down	30APR2015(21)	15:17	ND	ND	36.3	52	183

ND=Not Done; If the date is listed as ND, then the sort procedure will place the time point at the top of the list.

Listing 16.2.11 Physical Examination Abnormalities and Measurements

Part 1 of 2

Cohort	Patient ID	Visit	Study Date (Day)	Body System	Abnormal Findings
Cohort 1	3063-001	Baseline	17SEP2013(-1)	Ears	BOTH EARS DYSPLASTIC
			17SEP2013(-1)	Eyes	NO EYEBROWS NO EYELASHES
			17SEP2013(-1)	Mouth	THICK EVERTED LIPS
			17SEP2013(-1)	Skin Appearance	VERY DRY, PEELING, ECZEMATOUS
		Day 0	18SEP2013(0)	General Appearance	SIGNS OF ECTODERMAL DYSPLASIA
			18SEP2013(0)	Skin Appearance	VERY DRY, EXCEMATOUS
		Day 1	19SEP2013(1)	General Appearance	SIGNS OF ECTODERMAL DYSPLASIA
			19SEP2013(1)	Skin Appearance	VERY DRY
		Day 4	22SEP2013(4)	General Appearance	SIGNS OF ECTODERMAL DYSPLASIA
			22SEP2013(4)	Skin Appearance	VERY DRY
		Day 7	25SEP2013(7)	General Appearance	SIGNS OF ECTODERMAL DYSPLASIA
			25SEP2013(7)	Skin Appearance	VERY DRY
		Day 11	29SEP2013(11)	General Appearance	SIGNS OF ECTODERMAL DYSPLASIA
			29SEP2013(11)	Skin Appearance	DRY, PEELING
		Day 14	02OCT2013(14)	General Appearance	SIGNS OF ECTODERMAL DYSPLASIA
			02OCT2013(14)	Skin Appearance	DRY, SOME EYEBROWS AND EYELASHES VISIBLE
		Day 15	03OCT2013(15)	General Appearance	SIGNS OF ECTODERMAL DYSPLASIA
			03OCT2013(15)	Skin Appearance	DRY, EYEBROWS AND EYELASHES CLEARLY VISIBLE INCREASING AMOUNT OF HAIR
		Day 21	09OCT2013(21)	Ears	BOTH EARS DYSPLASTIC
			09OCT2013(21)	Eyes	SPARSE EYEBROWS
			09OCT2013(21)	Mouth	THICK, EVERTED LIPS
			09OCT2013(21)	Skin Appearance	DRY, BUT IMPROVED,NO ECZEMA
		Month 2	19NOV2013(62)	Ears	BOTH EARS DYPLASTIC
			19NOV2013(62)	Eyes	SPARSE EYEBROWS AND EYELASHES
			19NOV2013(62)	Mouth	THICK, EVERTED LIPS
			19NOV2013(62)	Skin Appearance	STILL DRY, NO ECZEMA
		Month 4	16JAN2014(120)	Ears	BOTH EARS STILL A LITTLE DYSPLASTIC
			16JAN2014(120)	Eyes	SPARSE EYEBROWS ANS EYELASHES
			16JAN2014(120)	Mouth	THICK, EVERTED LIPS
		Month 6	24MAR2014(187)	Ears	BOTH A LITTLE DYSPLASTIC
			24MAR2014(187)	Eyes	SPARSE EYEBROWS AND EYELASHES
			24MAR2014(187)	Mouth	THICK, SLIGHTLY EVERTED LIPS
Cohort 1	1012-001	Baseline	26NOV2013(-6)	Mouth	RETRUDED CHIN
			26NOV2013(-6)	Skin Appearance	THIN SCALP HAIR, THIN EYE BROWS, DRY
		Month 2	22JAN2014(51)	Skin Appearance	HEMANGIOMA ON NECK, THIN HAIR

ND=Not Done

Listing 16.2.11 Physical Examination Abnormalities and Measurements
Part 1 of 2

Cohort	Patient ID	Visit	Study Date (Day)	Body System	Abnormal Findings
Cohort 1	1012-001	Month 4	20MAR2014(108)	Skin Appearance	SPARSE SCALP HAIR & EYEBROWS
		Month 6	30MAY2014(179)	Skin Appearance	PATCHES OF ECZEMA, THIN HAIR AND EYEBROWS
Cohort 1	1068-001	Baseline	02MAR2014(-3)	Eyes	VERY SPARSE EYELASHES AND NO EYEBROWS SEEN
			02MAR2014(-3)	Mouth	THIN ALVEOLAR RIDGE ON MANDIBLE WITH MIDLINE WHITE NODULE (? TOOTH BUD); RETROGNATHIA; THIN ALVEOLAR RIDGE ON MAXILLA AS WELL
			02MAR2014(-3)	Skin Appearance	THIN SKIN AND VISIBLE VEINS; REDNESS OF EARS
		Day 0	05MAR2014(0)	General Appearance	FEATURES OF XLHED, UNCHANGED FROM PREVIOUS EXAM
			05MAR2014(0)	Skin Appearance	PALE, VISIBLE VEINS; DRY; UNCHANGED FROM PREVIOUS EXAM
		Day 1	06MAR2014(1)	General Appearance	FEATURES OF XLHED, UNCHANGED
			06MAR2014(1)	Skin Appearance	PALE, VISIBLE VEINS
		Day 4	09MAR2014(4)	General Appearance	FEATURES CONSISTENT WITH XLHED
			09MAR2014(4)	Skin Appearance	SKIN BIOPSY SCAB, LEFT LATERAL THIGH
		Day 7	12MAR2014(7)	General Appearance	PHYSICAL SIGNS OF XLHED; IV ON SCALP
			12MAR2014(7)	Skin Appearance	SKIN BIOPSY SCAB ON LEFT LATERAL THIGH
		Day 11	16MAR2014(11)	General Appearance	PHYSICAL FEATURES OF XLHED, NO CHANGE
			16MAR2014(11)	Skin Appearance	PALE, VISIBLE VEINS AND CUTIS MARMORATA, NO CHANGE
		Day 14	19MAR2014(14)	General Appearance	FEATURES OF XLHED, UNCHANGED
			19MAR2014(14)	Skin Appearance	PALE, CUTIS MARMORATA, UNCHANGED; SKIN BX SITES ON LEFT AND RIGHT THIGHS, HEALING WELL
		Day 15	20MAR2014(15)	General Appearance	FEATURES OF XLHED, UNCHANGED FROM PRIOR EXAMS
			20MAR2014(15)	Skin Appearance	PALE, VISIBLE VEINS, UNCHANGED; SKIN BIOPSY SITE ON RIGHT THIGH
		Day 21	26MAR2014(21)	Head	NORMOCEPHALIC; FACIAL FEATURES C/W XLHED
			26MAR2014(21)	Eyes	FEW EYELASHES AND SPARSE EYEBROWS; SLIGHT YELLOW DRAINAGE BOTH EYES; NASAL CONGESTION
			26MAR2014(21)	Skin Appearance	PALE VISIBLE VEINS WITHOUT CHANGE FROM PRIOR EXAMS
		Month 2	22APR2014(48)	Eyes	NO EYEBROWS, SPARSE EYELASHES, PERRL, EOMI
			22APR2014(48)	Mouth	THIN ALVEOLAR RIDGES, BONY RIDGE IN MIDLINE OF MANDIBLE (NO CHANGE FROM PREVIOUS EXAM)
			22APR2014(48)	Skin Appearance	PALE, VISIBLE VEINS, SOFT AND SMOOTH SKIN
		Month 4	24JUN2014(111)	Eyes	NO EYEBROWS; EYELASHES PRESENT
			24JUN2014(111)	Mouth	POINTED AREAS ON UPPER ALVEOLAR RIDGE, QUESTION IF THESE ARE CANINE TEETH, ALVEOLAR RIDGE OTHERWISE THIN
			24JUN2014(111)	Skin Appearance	SOFT, SMOOTH; CUTIS MARMORATA; 2 BIOPSY SITES ON RIGHT THIGH, 1 BIOPSY SITE ON LEFT THIGH; DIAPER RASH PRESENT
		Month 6	26AUG2014(174)	Eyes	NO EYEBROWS; SPARSE EYELASHES

ND=Not Done

Listing 16.2.11 Physical Examination Abnormalities and Measurements
Part 1 of 2

Cohort	Patient ID	Visit	Study Date (Day)	Body System	Abnormal Findings
Cohort 1	1068-001	Month 6	26AUG2014(174)	Mouth	NO TEETH; THIN ALVEOLAR RIDGES; 2 UPPER AND 2 LOWER BULGES ON ALVEOLAR RIDGE, QUESTIONABLE WHETHER CANINES
			26AUG2014(174)	Skin Appearance	PALE, VISIBLE BLOOD VESSELS UNDER SKIN; CUTIS MARMORATA; SOFT SKIN; 2 BIOPSY SITES ON RIGHT THIGH, 1 BIOPSY SITE ON LEFT THIGH; 2.5 X 2 CM VASCULAR BIRTHMARK ON MID-BACK, SEEN BEFORE
Cohort 2	3064-001	Baseline	07MAY2014(-2)	Eyes	PERIORBITAL HYPERPIGMENTATION.
			07MAY2014(-2)	Skin Appearance	DRY AND FLAKING SKIN ON TORSO
		Day 0	09MAY2014(0)	Skin Appearance	DRY AND FLAKING ON TORSO
		Day 1	10MAY2014(1)	Skin Appearance	DRY AND FLAKING ON TORSO
		Day 4	13MAY2014(4)	Skin Appearance	DRY AND FLAKING SKIN ON TORSO
		Day 7	16MAY2014(7)	Skin Appearance	DRY AND FLAKING SKIN ON TORSO
		Day 11	20MAY2014(11)	Skin Appearance	DRY AND FLAKY SKIN TO TORSO.
		Day 14	23MAY2014(14)	Skin Appearance	DRY AND FLAKY SKIN ON TORSO
		Day 15	24MAY2014(15)	Skin Appearance	DRY AND FLAKY SKIN ON TORSO
		Day 21	30MAY2014(21)	Skin Appearance	DRY AND FLAKING SKIN ON TORSO
		Month 4	01SEP2014(115)	Head	SPARSE HAIR.
			01SEP2014(115)	Eyes	WRINKLING AND PIGMENTATION AROUND EYES
		Month 6	03NOV2014(178)	Head	DRY PATCH ON LEFT SIDE OF SCALP. HAIR A BIT SPARSE LATERALLY
			03NOV2014(178)	Eyes	HYPERPIGMENTATION AROUND EYES AND WRINKLING AROUND EYES.
			03NOV2014(178)	Skin Appearance	FLAKY DRY SKIN ON FEET, OTHERWISE GOOD SKIN INTEGRITY
Cohort 2	3005-001	Baseline	31JUL2014(-4)	Eyes	REDUCED MEIBOMIAN GLANDS- REDUCED TEARS
			31JUL2014(-4)	Mouth	EVERTED LIPS-MICROSTOMIA
		Day 21	25AUG2014(21)	Eyes	NO EYELASHES-NO EYEBROWS
			25AUG2014(21)	Skin Appearance	ERYTHEMATIUS PLAQUES ON CHEEKS-"ECZEMATIFORM LESIONS
		Month 2	08SEP2014(35)	Head	MILD OCCIPITAL RIGHT PLAGIOCEPHALY. LEFT OCCIPITAL AND BILATERAL CERVICAL ADENOPATHY < 1CM, NOT CLINICALLY SIGNIFICANT.HAIR GROWTH.
			08SEP2014(35)	Ears	PARTIAL HYPOPLASIA OF RIGHT EAR
			08SEP2014(35)	Eyes	EYELASHES GROWTH
			08SEP2014(35)	Mouth	MILD RETROGNATHIA
		Month 4	10NOV2014(98)	Eyes	FEW EYELASHES AND BROWS
			10NOV2014(98)	Mouth	SMALL
			10NOV2014(98)	Skin Appearance	REDUCED SWEATING
		Month 6	12JAN2015(161)	Skin Appearance	ECZEMATOUS DIFFUSE LESIONS

ND=Not Done

Listing 16.2.11 Physical Examination Abnormalities and Measurements
Part 1 of 2

Cohort	Patient ID	Visit	Study Date (Day)	Body System	Abnormal Findings
Cohort 2	3063-002	Baseline	29OCT2014(-4)	Head	SLIGHTLY DYSPLASTIC JAWS
			29OCT2014(-4)	Eyes	SPARSE EYEBROWS AND EYELASHES
			29OCT2014(-4)	Mouth	EVERTED LIPS
			29OCT2014(-4)	Skin Appearance	VERY DRY, SCALY SKIN
		Day 0	02NOV2014(0)	General Appearance	CLINICAL SIGNS OF ECTODERMAL DYSPLASIA
			02NOV2014(0)	Skin Appearance	DRY AND SCALY
		Day 1	03NOV2014(1)	General Appearance	CLINICAL SIGNS OF XLHED
			03NOV2014(1)	Skin Appearance	DRY AND SCALY
		Day 4	05NOV2014(3)	General Appearance	CLINICAL SIGNS OF XLHED
			05NOV2014(3)	Skin Appearance	PEELING
		Day 7	09NOV2014(7)	General Appearance	CLINICAL SIGNS OF XLHED
			09NOV2014(7)	Skin Appearance	PEELING, NOT AS DRY AS BEFORE
		Day 11	14NOV2014(12)	General Appearance	CLINICAL SIGNS OF XLHED
		Day 14	16NOV2014(14)	General Appearance	CLINICAL SIGNS OF XLHED
		Day 15	17NOV2014(15)	General Appearance	SIGNS OF XLHED, MILD PHENOTYPE
		Day 21	23NOV2014(21)	Head	SLIGHTLY DYSPLASTIC JAWS
			23NOV2014(21)	Eyes	SPARSE EYEBROWS
			23NOV2014(21)	Mouth	EVERTED LIPS
		Month 2	18DEC2014(46)	Head	SLIGHTLY DYSPLASTIC JAWS
			18DEC2014(46)	Mouth	EVERTED LIPS
		Month 4	23FEB2015(113)	Head	SLIGHTLY HYPOPLASTIC JAWS
			23FEB2015(113)	Mouth	EVERTED LIPS
		Month 6	21APR2015(170)	Head	SLIGHTLY HYPOPLASTIC UPPER JAW
Cohort 2	3063-003	Baseline	24NOV2014(-2)	Head	HYPOPLASTIC MANDIBLE
			24NOV2014(-2)	Ears	BOTH EARS DYSPLASTIC
			24NOV2014(-2)	Eyes	SPARSE EYEBROWS AND EYELASHES
			24NOV2014(-2)	Mouth	EVERTED LIPS, ORAL THRUSH
			24NOV2014(-2)	Skin Appearance	VERY DRY, ECZEMATOUS, PEELING
		Day 0	26NOV2014(0)	General Appearance	CLINICAL SIGNS OF XLHED
			26NOV2014(0)	Skin Appearance	VERY DRY, ECZEMATOUS, PEELING
		Day 1	27NOV2014(1)	General Appearance	CLINICAL SIGNS OF XLHED
			27NOV2014(1)	Skin Appearance	VERY DRY, ECZEMATOUS, PEELING
		Day 4	01DEC2014(5)	General Appearance	CLINICAL SIGNS OF XLHED
			01DEC2014(5)	Skin Appearance	VERY DRY, ECZEMATOUS, PEELING
		Day 7	04DEC2014(8)	General Appearance	CLINICAL SIGNS OF XLHED

ND=Not Done

Listing 16.2.11 Physical Examination Abnormalities and Measurements
Part 1 of 2

Cohort	Patient ID	Visit	Study Date (Day)	Body System	Abnormal Findings
Cohort 2	3063-003	Day 7	04DEC2014(8)	Skin Appearance	STILL DRY AND PEELING BUT IMPROVED
		Day 11	07DEC2014(11)	General Appearance	CLINICAL SIGNS OF XLHED
			07DEC2014(11)	Skin Appearance	DRY, SIGNIFICANTLY IMPROVED
		Day 14	10DEC2014(14)	General Appearance	CLINICAL SIGNS OF XLHED
			10DEC2014(14)	Skin Appearance	DRY, SIGNIFICANTLY IMPROVED
		Day 15	11DEC2014(15)	General Appearance	CLINICAL SIGNS OF XLHED
			11DEC2014(15)	Skin Appearance	DRY
		Day 21	17DEC2014(21)	Head	HYPOPLASTIC MANDIBLE
			17DEC2014(21)	Ears	BOTH EARS DYSPLASTIC
			17DEC2014(21)	Eyes	SPARSE EYEBROWS
			17DEC2014(21)	Mouth	EVERTED LIPS
			17DEC2014(21)	Skin Appearance	DRY, PARTIALLY SCALY
		Month 2	15JAN2015(50)	Head	HYPOPLASITC MANDIBLE
			15JAN2015(50)	Ears	BOTH EARS DYSPLASTIC
			15JAN2015(50)	Eyes	SPARSE EYEBROWS
			15JAN2015(50)	Mouth	EVERTED LIPS
		Month 4	17MAR2015(111)	Head	HYPOPLASTIC MANDIBLE
			17MAR2015(111)	Ears	SLIGHTLY DYSPLASTIC
			17MAR2015(111)	Eyes	SPARSE EYEBROWS
			17MAR2015(111)	Mouth	EVERTED LIPS
			17MAR2015(111)	Abdomen	UMBILICAL HERNIA, DIAMETER 0.8 CM
		Month 6	19MAY2015(174)	Head	HYPOPLASTIC MANDIBLE
			19MAY2015(174)	Ears	PROTRUDING
			19MAY2015(174)	Eyes	SPARSE EYEBROWS
			19MAY2015(174)	Mouth	SLIGHTLY EVERTED LIPS
			19MAY2015(174)	Abdomen	UMBILICAL HERNIA, DIAMETER 0.5 CM
Cohort 2	3063-004	Baseline	02JAN2015(-3)	Head	HYPOPLASTIC MANDIBLE
			02JAN2015(-3)	Eyes	SPARSE EYEBROWS AND EYELASHES
			02JAN2015(-3)	Mouth	EVERTED LIPS
			02JAN2015(-3)	Skin Appearance	VERY DRY, GLOSSY, PARTIALLY PEELING
		Day 0	05JAN2015(0)	General Appearance	CLINICAL SIGNS OF XLHED
			05JAN2015(0)	Skin Appearance	VERY DRY, SCALY
		Day 1	06JAN2015(1)	General Appearance	CLINICAL SIGNS OF XLHED
			06JAN2015(1)	Skin Appearance	VERY DRY, PEELING
		Day 4	08JAN2015(3)	General Appearance	CLINICAL SIGNS OF ECTODERMAL DYSPLASIA

ND=Not Done

Listing 16.2.11 Physical Examination Abnormalities and Measurements
Part 1 of 2

Cohort	Patient ID	Visit	Study Date (Day)	Body System	Abnormal Findings
Cohort 2	3063-004	Day 4	08JAN2015(3)	Skin Appearance	DRY, PEELING
		Day 7	12JAN2015(7)	General Appearance	CLINICAL SIGNS OF XLHED
			12JAN2015(7)	Skin Appearance	DRY, PEELING
		Day 11	15JAN2015(10)	General Appearance	CLINICAL SIGNS OF XLHED
			15JAN2015(10)	Skin Appearance	DRY, PEELING
		Day 14	19JAN2015(14)	General Appearance	CLINICAL SIGNS OF XLHED
			19JAN2015(14)	Skin Appearance	DRY, PEELING
		Day 15	20JAN2015(15)	General Appearance	CLINICAL SIGNS OF XLHED
			20JAN2015(15)	Skin Appearance	DRY, PEELING
		Day 21	26JAN2015(21)	Head	HYPOPLASTIC MANDIBLE
			26JAN2015(21)	Eyes	SPARSE EYEBROWS AND EYELASHES
			26JAN2015(21)	Mouth	EVERTED LIPS
		Month 2	27FEB2015(53)	Head	HYPOPLASTIC MANDIBLE
			27FEB2015(53)	Eyes	SPARSE EYEBROWS
			27FEB2015(53)	Mouth	EVERTED LIPS
		Month 4	30APR2015(115)	Head	HYPOPLASTIC MANDIBLE
			30APR2015(115)	Eyes	SPARSE EYEBROWS
			30APR2015(115)	Mouth	EVERTED LIPS
		Month 6	29JUN2015(175)	Head	HYPOPLASTIC MANDIBLE
			29JUN2015(175)	Mouth	EVERTED LIPS
			29JUN2015(175)	Skin Appearance	DRY, A FEW ECZEMATOUS AREAS
Cohort 3	1068-002	Baseline	25FEB2015(-2)	Eyes	NO EYEBROWS, SLIGHTLY DARKER SKIN AROUND EYES, EYELASHES PRESENT
			25FEB2015(-2)	Mouth	THRUSH, FULL LIPS, REDNESS OF TONGUE WITH WHITE PLAQUES, THIN LOWER ALVEOLAR RIDGE, MANDIBLE MIDLINE, POSSIBLE UPPER CENTRAL INCISORS PRESENT AND POSSIBLE LOWER TEETH ON EACH SIDE WITH BULGES ON ALVEO
			25FEB2015(-2)	Skin Appearance	DRY PATCHES, NIPPLES ARE PRESENT
		Day 0	27FEB2015(0)	Skin Appearance	SLIGHTLY DRY
		Day 1	28FEB2015(1)	Skin Appearance	SLIGHT DIAPER RASH, SKIN OTHERWISE NORMAL
		Day 4	03MAR2015(4)	Skin Appearance	MILD DIAPER RASH, IMPROVING BIOPSY SITES ON LEFT AND RIGHT THIGHS
		Day 7	06MAR2015(7)	Skin Appearance	EYES WITH RED EYELIDS; PUFFY LIDS; DIAPER RASH IMPROVING
		Day 11	10MAR2015(11)	Skin Appearance	EYES MUCH IMPROVED; SLIGHT CRUST AROUND RIGHT EYE; BIOPSY SITES ON LEFT AND RIGHT THIGHS HEALED; SLIGHT RED DIAPER RASH
		Day 14	13MAR2015(14)	Skin Appearance	EYES IMPROVING, STILL SLIGHT REDNESS OF EYELIDS; DIAPER RASH MINIMAL
		Day 15	14MAR2015(15)	Skin Appearance	SLIGHT BLOTCHY RASH ON FACE WITH CRYING; EYES IMPROVED; STILL HAS EXCORIATED AREA ON BUTTOCKS AND USING TRIPLE PASTE

ND=Not Done

Listing 16.2.11 Physical Examination Abnormalities and Measurements
Part 1 of 2

Cohort	Patient ID	Visit	Study Date (Day)	Body System	Abnormal Findings
Cohort 3	1068-002	Day 21	20MAR2015(21)	Eyes	NO VISIBLE EYEBROWS; A FEW EYELASHES SEEN; REDNESS OF EYELIDS IMPROVED
			20MAR2015(21)	Skin Appearance	SLIGHT DRYNESS ON HEAD, OTHERWISE NORMAL; DIAPER RASH RESOLVED
		Month 2	17APR2015(49)	Eyes	SPARSE EYEBROWS; EYELIDS PUFFY; EYELASHES PRESENT, BUT SPARSE
			17APR2015(49)	Mouth	THIN LOWER ALVEOLAR RIDGE
			17APR2015(49)	Skin Appearance	DRY SCALP; SPARSE SCALP HAIR BUT INCREASED FROM LAST EXAM
		Month 4	19JUN2015(112)	Eyes	EYELASHES PRESENT TOP AND BOTTOM, SPARSE IN BUT SOME ARE ~3 MM IN LENGTH; EYEBROWS PRESENT, BUT MORE HAIR MEDIALLY
			19JUN2015(112)	Mouth	THIN LOWER ALVEOLAR RIDGE, NO ERUPTED TEETH YET
			19JUN2015(112)	Skin Appearance	SLIGHT DRYNESS ON SCALP, A FEW RED SPOTS ON THE BACK OF THE HEAD
		Month 6	12AUG2015(166)	Eyes	SPARSE EYEBROWS LATERALLY, EYELASHES PRESENT UPPER AND LOWER BILATERALLY
			12AUG2015(166)	Mouth	UPPER RIDGE WITH BULGES CENTRALLY, LOWER RIDGE THIN CENTRALLY, BUT WITH 2 BULGES LATERALLY
			12AUG2015(166)	Skin Appearance	SCALP DRY ON TOP RIGHT SIDE AND HAS SCABS ON VERTEX FROM SCRATCHING, 2 AREAS OF DRY SKIN ON SHOULDERS BUT OTHERWISE CLEAR
Cohort 3	3064-002	Baseline	06APR2015(-3)	Ears	CRUMPLED AND OVERFOLDED
			06APR2015(-3)	Eyes	SPARSE BROWS AND LASHES
			06APR2015(-3)	Mouth	UNDERDEVELOPED ALVEOLAR RIDGES (PATCHY)
			06APR2015(-3)	Skin Appearance	DRY
		Day 0	09APR2015(0)	General Appearance	SPARSE HAIR, BROWS AND LASHES AS WITH XHED
			09APR2015(0)	Skin Appearance	DRY, PEELING.
		Day 1	10APR2015(1)	General Appearance	DRY SKIN AND FEATURES OF ECTODERMAL DYSPLASIA
			10APR2015(1)	Skin Appearance	DRY SKIN AND FEATURES OF ECTODERMAL DYSPLASIA.
		Day 4	13APR2015(4)	General Appearance	FEATURES OF H.E.D
			13APR2015(4)	Skin Appearance	SKIN LESS DRY
		Day 7	16APR2015(7)	General Appearance	FEATURES OF ECTODERMAL DYSPLASIA
			16APR2015(7)	Skin Appearance	SKIN LESS DRY
		Day 11	20APR2015(11)	General Appearance	FEATURES OF ECTODERMAL DYSPLASIA
			20APR2015(11)	Skin Appearance	DRY SKIN.SPARSE HAIR, EYEROWS AND LASHES.
		Day 14	23APR2015(14)	General Appearance	FEATURES OF ECTODERMAL DYSPLASIA
			23APR2015(14)	Skin Appearance	FEATURES OF ECTODERMAL DYSPLASIA
		Day 15	24APR2015(15)	General Appearance	FACIAL FEATURES OF HED
			24APR2015(15)	Skin Appearance	SKIN DRY. HAIR, BROWS AND LASHES SPARSE.
		Day 21	30APR2015(21)	Ears	SLIGHTLY CRUMPLED
			30APR2015(21)	Eyes	SPARSE BROWS/LASHES
			30APR2015(21)	Mouth	ABNORMAL ALVEOLAR RIDGE

ND=Not Done

Listing 16.2.11 Physical Examination Abnormalities and Measurements
Part 1 of 2

Cohort	Patient ID	Visit	Study Date (Day)	Body System	Abnormal Findings
Cohort 3	3064-002	Day 21	30APR2015(21)	Skin Appearance	DRY STILL. BETTER THAN ON ADMISSION. SPARSE SCALP HAIR. INTERMEDIATE.
		Month 2	01JUN2015(53)	Ears	FOLDED HELICES
			01JUN2015(53)	Eyes	DRY/FOLDED SKIN AROUND ORBITS /EYELIDS
			01JUN2015(53)	Mouth	UNDERDEVELOPED ALVEOLAR RIDGES (PATCHY)
			01JUN2015(53)	Skin Appearance	DRY SKIN ON FEET
			01JUN2015(53)	Pulmonary	SUB COSTAL RECESSIONS NOTED. SNUFFLY NASAL INHALATIONS
		Month 4	03AUG2015(116)	Ears	SLIGHTLY CRUMPLED
			03AUG2015(116)	Eyes	SPARSE EYEBROWS AND EYELASHES
			03AUG2015(116)	Mouth	NO TEETH. ABNORMAL ALVEOLAR RIDGE
			03AUG2015(116)	Skin Appearance	DRY,ECZEMATOUS PATCHES. SPARSE SCALP HAIR.
		Month 6	28SEP2015(172)	Head	MILD PLAGIOCEPHALY AND FINE HAIR
			28SEP2015(172)	Eyes	SPARSE EYEBROWS AND LASHES
			28SEP2015(172)	Mouth	UNDERDEVELOPED ALVEOLAR RIDGE. EVIDENCE OF DENTITION
			28SEP2015(172)	Skin Appearance	DRY SKIN TO FEET BILATERALLY. MILD ERYTHEMA TO ANTERIOR OF NECK SECONDARY TO SALIVATION
Siblings	3063-201	Enrollment	29OCT2014	General Appearance	CLINICAL SIGNS OF XLHED
			29OCT2014	Skin Appearance	DRY AND THIN,PERIOCULAR WRINKLES
	3063-202	Enrollment	25NOV2014	General Appearance	CLINICAL SIGNS OF XLHED
			25NOV2014	Skin Appearance	VERY DRY, ECZEMATOUS
	3064-201	Enrollment	01SEP2014	General Appearance	DRY HYPERPIGMENTED SKIN PERIORBITAL/INFRA ORAL. DRY MUCOSAL MEMBRANES.
			01SEP2014	Skin Appearance	MILD FLEXURAL ECZEMA WITH EXCORIATION ANTE CUBITAL FOSSA, BILATERALLY.

ND=Not Done

Listing 16.2.11 Physical Examination Abnormalities and Measurements

Part 2 of 2

Cohort	Patient ID	Date of Birth	Birth Weight (kg)	Visit	Study Date (Day)	Weight (kg)	Length (cm)	Head Circumference (cm)
Cohort 1	3063-001	15SEP2013	3.8	Baseline	17SEP2013(-1)	3.5	51.0	34.5
				Day 0	18SEP2013(0)	3.5		
				Day 1	19SEP2013(1)	3.4		
				Day 4	22SEP2013(4)	3.4		
				Day 7	25SEP2013(7)	3.6		
				Day 11	29SEP2013(11)	3.7		
				Day 14	02OCT2013(14)	3.8		
				Day 15	03OCT2013(15)	3.9		
				Day 21	09OCT2013(21)	4.1	53.5	36.7
				Month 2	19NOV2013(62)	5.8	60.0	39.7
				Month 4	16JAN2014(120)	6.6	65.0	42.2
				Month 6	24MAR2014(187)	7.7	69.0	43.5
Cohort 1	1012-001	19NOV2013	3.8	Baseline	26NOV2013(-6)	3.8	52.0	35.0
				Day 0	02DEC2013(0)	4.0		
				Day 1	03DEC2013(1)	4.1		
				Day 4	06DEC2013(4)	4.2		
				Day 7	09DEC2013(7)	4.3		
				Day 11	13DEC2013(11)	4.6		
				Day 14	16DEC2013(14)	4.7		
				Day 15	17DEC2013(15)	4.7		
				Day 21	23DEC2013(21)	4.9	61.5	37.0
				Month 2	22JAN2014(51)	5.6	61.0	38.5
				Month 4	20MAR2014(108)	6.4	64.5	41.0
				Month 6	30MAY2014(179)	7.2	70.0	42.5
Cohort 1	1068-001	20FEB2014	3.8	Baseline	02MAR2014(-3)	3.6	53.0	36.0
				Day 0	05MAR2014(0)	3.7		
				Day 1	06MAR2014(1)	3.7		
				Day 4	09MAR2014(4)	3.8		
				Day 7	12MAR2014(7)	3.8		
				Day 11	16MAR2014(11)	4.0		
				Day 14	19MAR2014(14)	4.1		
				Day 15	20MAR2014(15)	4.0		

ND=Not Done

Listing 16.2.11 Physical Examination Abnormalities and Measurements
Part 2 of 2

Cohort	Patient ID	Date of Birth	Birth Weight (kg)	Visit	Study Date (Day)	Weight (kg)	Length (cm)	Head Circumference (cm)
Cohort 1	1068-001	20FEB2014	3.8	Day 21	26MAR2014(21)	4.2	57.5	37.5
				Month 2	22APR2014(48)	4.8	59.0	39.0
				Month 4	24JUN2014(111)	6.4	64.0	43.5
				Month 6	26AUG2014(174)	6.8	66.5	44.0
Cohort 2	3064-001	29APR2014	3.3	Baseline	07MAY2014(-2)	3.2	50.5	34.4
				Day 0	09MAY2014(0)	3.3		
				Day 1	10MAY2014(1)	3.4		
				Day 4	13MAY2014(4)	3.3		
				Day 7	16MAY2014(7)	3.4		
				Day 11	20MAY2014(11)	3.5		
				Day 14	23MAY2014(14)	3.7		
				Day 15	24MAY2014(15)	ND		
				Day 21	30MAY2014(21)	3.9	54.3	36.1
				Month 2	30JUN2014(52)	4.7		38.4
				Month 4	01SEP2014(115)	6.2	64.0	43.0
				Month 6	03NOV2014(178)	7.3	66.5	42.0
Cohort 2	3005-001	08JUL2014	3.0	Baseline	31JUL2014(-4)	3.5	52.5	37.0
				Day 0	04AUG2014(0)	3.7		
				Day 1	05AUG2014(1)	3.7		
				Day 4	08AUG2014(4)	3.9		
				Day 7	11AUG2014(7)	4.0		
				Day 11	14AUG2014(10)	4.1		
				Day 14	18AUG2014(14)	4.2		
				Day 15	19AUG2014(15)	4.2		
				Day 21	25AUG2014(21)	4.2	59.5	39.0
				Month 2	08SEP2014(35)	4.8	58.0	40.5
				Month 4	10NOV2014(98)	6.5	65.5	42.5
				Month 6	12JAN2015(161)	8.3	70.0	46.0
Cohort 2	3063-002	21OCT2014	3.1	Baseline	29OCT2014(-4)	3.0	49.0	34.5
				Day 0	02NOV2014(0)	3.1		
				Day 1	03NOV2014(1)	3.1		

ND=Not Done

Listing 16.2.11 Physical Examination Abnormalities and Measurements
Part 2 of 2

Cohort	Patient ID	Date of Birth	Birth Weight (kg)	Visit	Study Date (Day)	Weight (kg)	Length (cm)	Head Circumference (cm)
Cohort 2	3063-002	21OCT2014	3.1	Day 4	05NOV2014(3)	3.3		
				Day 7	09NOV2014(7)	3.3		
				Day 11	14NOV2014(12)	3.4		
				Day 14	16NOV2014(14)	3.5		
				Day 15	17NOV2014(15)	3.5		
				Day 21	23NOV2014(21)	3.8	51.6	36.5
				Month 2	18DEC2014(46)	4.6	55.0	38.0
				Month 4	23FEB2015(113)	6.3	63.5	40.5
				Month 6	21APR2015(170)	6.5	65.0	42.5
Cohort 2	3063-003	17NOV2014	2.9	Baseline	24NOV2014(-2)	2.8	49.0	33.5
				Day 0	26NOV2014(0)	2.8		
				Day 1	27NOV2014(1)	2.9		
				Day 4	01DEC2014(5)	3.0		
				Day 7	04DEC2014(8)	3.2		
				Day 11	07DEC2014(11)	3.2		
				Day 14	10DEC2014(14)	3.3		
				Day 15	11DEC2014(15)	3.4		
				Day 21	17DEC2014(21)	3.4	55.0	35.5
				Month 2	15JAN2015(50)	4.3	58.5	37.5
				Month 4	17MAR2015(111)	5.9	61.0	39.0
				Month 6	19MAY2015(174)	7.1	70.0	40.3
Cohort 2	3063-004	31DEC2014	2.7	Baseline	02JAN2015(-3)	2.6	47.0	33.5
				Day 0	05JAN2015(0)	2.7		
				Day 1	06JAN2015(1)	2.7		
				Day 4	08JAN2015(3)	2.7		
				Day 7	12JAN2015(7)	2.7		
				Day 11	15JAN2015(10)	2.9		
				Day 14	19JAN2015(14)	3.1		
				Day 15	20JAN2015(15)	3.1		
				Day 21	26JAN2015(21)	3.3	51.0	35.0
				Month 2	27FEB2015(53)	4.3	54.5	38.0
				Month 4	30APR2015(115)	5.9	61.9	40.4

ND=Not Done

Listing 16.2.11 Physical Examination Abnormalities and Measurements
Part 2 of 2

Cohort	Patient ID	Date of Birth	Birth Weight (kg)	Visit	Study Date (Day)	Weight (kg)	Length (cm)	Head Circumference (cm)
Cohort 2	3063-004	31DEC2014	2.7	Month 6	29JUN2015(175)	6.8	65.8	43.0
Cohort 3	1068-002	15FEB2015	4.0	Baseline	25FEB2015(-2)	3.8	55.5	37.2
				Day 0	27FEB2015(0)	3.8		
				Day 1	28FEB2015(1)	3.8		
				Day 4	03MAR2015(4)	4.2		
				Day 7	06MAR2015(7)	4.0		
				Day 11	10MAR2015(11)	4.1		
				Day 14	13MAR2015(14)	4.2		
				Day 15	14MAR2015(15)	4.3		
				Day 21	20MAR2015(21)	4.4	61.0	38.5
				Month 2	17APR2015(49)	4.6	60.0	40.0
				Month 4	19JUN2015(112)	5.8	66.3	42.0
				Month 6	12AUG2015(166)	6.8	68.1	43.5
Cohort 3	3064-002	30MAR2015	3.2	Baseline	06APR2015(-3)	3.1	48.5	34.0
				Day 0	09APR2015(0)	ND		
				Day 1	10APR2015(1)	ND		
				Day 4	13APR2015(4)	ND		
				Day 7	16APR2015(7)	ND		
				Day 11	20APR2015(11)	ND		
				Day 14	23APR2015(14)	ND		
				Day 15	24APR2015(15)	3.7		
				Day 21	30APR2015(21)	4.0	53.3	35.0
				Month 2	01JUN2015(53)	5.0	56.9	39.0
				Month 4	03AUG2015(116)	6.6	61.5	41.2
				Month 6	28SEP2015(172)	7.8	67.0	43.0

ND=Not Done

Appendix 16.3- Case Report Forms for Deaths, SAEs, and Withdrawals

Available Upon Request.

Appendix 16.4- DSMB Charter and Meeting Minutes

DSMB Charter
18 Jun 2013

Data Safety Monitoring Committee Charter

18JUN2013

Clinical Protocol

A Phase 2 open-label, dose-escalation study to evaluate the safety, pharmacokinetics, immunogenicity and pharmacodynamics/efficacy of EDI200, an EDA-A1 replacement protein, administered to male infants with X-Linked Hypohidrotic Ectodermal Dysplasia (XLHED)

Protocol ECP-002, Version 18JUN2013

Investigational Product: EDI200

Sponsor:

Edimer Pharmaceuticals, Inc.
55 Cambridge Parkway
Suite 102W
Cambridge MA 02142

Table of Contents

1. INTRODUCTION

This charter is for the Data Safety Monitoring Board (DSMB) for Edimer Protocol ECP002 "A Phase 2 open-label, dose-escalation study to evaluate the safety, pharmacokinetics, immunogenicity and pharmacodynamics/efficacy of EDI200, an EDA-A1 replacement protein, administered to male infants with X-Linked Hypohidrotic Ectodermal Dysplasia (XLHED)." It identifies the membership and describes the members' roles and responsibilities. The charter describes the DSMB relationship to other study entities, plan for communication and procedures for ensuring confidentiality. It also outlines the purpose, timing and procedures for meetings. Appendices contain the study protocols including amendments, informed consent forms, case report forms, specifications for presentations of data, and contact persons relevant to the trial and the DSMB.

Definitions and abbreviations to be used in this document:

Adverse Event (AE) – An adverse event (AE) is any reaction, side effect, or other untoward event (signs, symptoms, or changes in laboratory data) associated with participation in this study, whether or not the event is considered related to the study or any of the procedures being conducted.

Data Monitoring Committee (DSMB) - A group of individuals with pertinent expertise that reviews on a regular basis accumulating data from one or more ongoing clinical trials.

Contract Research Organization (CRO) – an entity that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the Food and Drug Administration.

Sponsor – an entity that takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.

2. ROLE OF THE COMMITTEE

The DSMB is responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of interventions during the trial, and for monitoring the overall conduct of the clinical trial. The DSMB will provide recommendations about stopping or continuing the trial. They will make recommendations about cohort dose escalation based on safety and exposure results.

At the scheduled DSMB review meetings, detailed safety reviews will be provided to the DSMB including: adverse events, concomitant medications, infusion/injection site reactions, physical examination, weights and vital signs, and all PK and safety laboratory values. Reports of these data, as well as information related to trial conduct and progress, will be prepared prior to each meeting. All safety laboratory studies will be done at the study site and available to the DSMB in real time. The data will be formatted according to the specifications in Appendix C of these guidelines.

DSMB Reviews

1. Reviews related to dosing of cohorts

    a. Prior to dosing of subjects in XLHED neonate cohort 1, the DSMB will have reviewed the safety and PK data from XLHED adult cohort 1 subjects dosed at the same 3 mg/kg/dose and the same 5 dose regimen.

    b. Following the dosing of subjects in XLHED neonate cohort 1, the DSMB will conduct a formal safety, tolerability and PK data review from that cohort to inform dose escalation in XLHED neonate cohort 2. The cohort 1 PK data review is intended to confirm that the exposure levels in the cohort as a whole and for each subject were within the limits associated with safe study drug administration in the preclinical GLP toxicology studies, and that the expected exposure with dose escalation in cohort 2 will remain in the range that is safe and well tolerated. Prior to the dosing of XLHED neonates in cohort 2, the DSMB also will have reviewed the safety and PK data from XLHED adult cohort 2 subjects dosed at the same 10 mg/kg/dose and the same 5 dose regimen.

    c. Once all subjects in a cohort have received their IV dosing, the DSMB will review safety, tolerability and PK data.

2. Unscheduled reviews related to safety findings and study stopping criteria

Unscheduled DSMB reviews will take place as outlined in Section 3.3.4 – 3.3.7 of the protocol for single or accumulated adverse events.

    a. Subject Dosing

    All AE and safety laboratory results will be available to the Medical Monitor, Principal Investigator and DSMB in real time. Unscheduled meetings may be held related to stopping dosing for a study subject based upon review of these data. If the discovery of a new adverse event related to study drug raises concerns over the safety of its continued administration to subjects, the sponsor or designee will take immediate steps to notify the DSMB, the regulatory authorities and all the investigators participating in clinical studies of the study drug.

b. Cohort Stopping Criteria

The study design has only one cohort being dosed with study drug at any given time. In the case where cohort dosing has been suspended (per protocol section 3.3.6), DSMB review of the adverse events with the Medical Monitor, study Principal Investigator and Sponsor will be required prior to discussing with a subject's family the option of restarting study drug or to enrolling additional subjects in the cohort. Missed doses will not be made up. Any subject missing two consecutive doses will not be restarted on treatment, will not be considered to have completed the dosing regimen, but will have all study follow-up visits as originally scheduled. If the DSMB safety review concludes that cohort dosing may continue, an additional subject may be added to the cohort for each subject that does not complete the dosing regimen.

In the case where a DSMB safety review concludes that a cohort should not continue dosing, no additional doses will be administered to subjects in that cohort, no additional subjects will be enrolled in that cohort, and all follow-up visits for enrolled subjects will occur as originally scheduled. The Sponsor will notify both the FDA and the local IRB/IEC of the action taken. The scheduled dose escalation cohorts will be suspended, although a more conservative dose escalation strategy may be considered for a subsequent cohort, requiring DSMB, relevant Competent National Authorities and study site IRB/IEC approval.

c. Study Stopping Criteria

The Sponsor and/or the DSMB have the right to close this study at any time for safety or administrative reasons, with timely notification of the relevant Competent National Authorities.

Permanent halting of dosing in any cohort by the DSMB related to safety concerns will trigger an automatic review of study termination by the DSMB in communication with the Medical Monitor, study Principal Investigator, and Sponsor. If it is determined that study dosing should be terminated, all follow-up visits will occur as originally scheduled for subjects having received one or more doses of study drug. Study Sponsor assumes responsibility for reporting premature study termination to all regulatory authorities and institutional review boards.

3. <u>End of study</u>

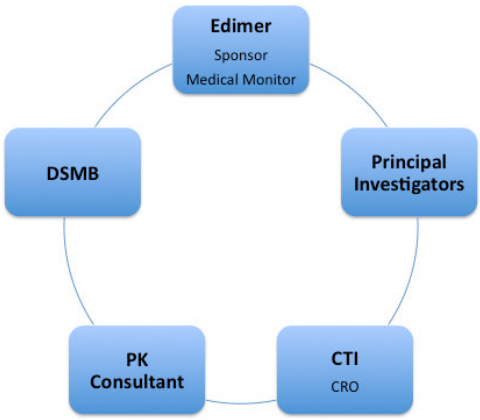
At the end of the Study, the DSMB will review and summarize all study safety data. DSMB summaries will be provided in a timely fashion to the Sponsor.

The DSMB may modify the timing of meetings based on subject enrollment or other factors they deem appropriate.

3. COMMITTEE MEMBERSHIP AND RESPONSIBILTIES

3.1 Organizational Diagram

The following diagram shows the relationship between the DSMB and other functional areas/groups involved in the trial.



3.2 Members

The DSMB is an independent multidisciplinary group consisting of clinicians, biostatisticians and other relevant personnel that, collectively, has experience in the management of patients with rare genetic disorders and in the conduct and monitoring of randomized clinical trials.

Chair – Michael J. Corwin, MD
Member - Stephen Pelton, MD
Member – John Rogus
Member – Christian Poets, MD

Contact numbers and addresses are provided in Appendix D of these guidelines. Each member's *curriculum vitae* will be available in the Sponsor's files and will be provided to any regulatory agency that requests a copy.

3.3 Responsibilities

DSMB members are responsible for maintaining strict confidentiality of the study data. DSMB members will not share any unblinded data with any individual outside of the DSMB and will not share any study data or such information about the study with any individual outside the study.

DSMB members are expected, insofar as possible, to participate actively in each review meeting, including the in-person meetings as well as teleconference and/or videoconference meetings.

It is expected that DSMB members will maintain their scientific objectivity throughout the course of the trial and will consistently deploy their best scientific judgment and the highest ethical standards in making recommendations regarding the conduct of the trial.

It is anticipated that minutes will be prepared and maintained for each meeting, in-person meetings as well as teleconference and/or videoconference meetings. Each member of the DSMB has the responsibility to read the draft minutes and make editing recommendations such that the minutes reflect accurately what transpired at the meeting. Following each meeting the DSMB chair will transmit the recommendations of the committee to the Sponsor. At the conclusion of the trial, all minutes of the DSMB meetings will be transmitted to the Sponsor (see Section 5.3 below). A final DSMB meeting will be held at the conclusion of the study for the Sponsor to review the study findings with the DSMB.

3.4 Financial Disclosure and Conflict of Interest

The DSMB will be responsible for deciding whether consultancies and/or financial interests of the members materially impact on objectivity. This decision is to be based on the reasonable belief that their objectivity is not in doubt. Members of the DSMB will be responsible for advising the Chair of the DSMB of any changes in financial interest in pharmaceutical companies, biotech companies, or contract research organizations, including consultancies. Members of the DSMB who develop potential or significant perceived conflicts of interest that materially impact on objectivity will be asked to resign from the DSMB.

3.5 Duration of DSMB Membership

The duration of DSMB membership will cover the duration of the clinical trial through the Study Completion Meeting. Should a member have to resign, the reason must be indicated in writing to the Chair of the DSMB. If a member leaves the DSMB or is asked to resign due to a conflict of interest, a replacement will be sought, and will be approved by the Sponsor.

4. COMMITTEE MEETINGS

4.1 Organizational Meeting

An organizational meeting will be held to establish the Committee formally and to acquaint the DSMB members thoroughly with the protocol, case report forms and the tables that will be provided for the meetings (specifications appear as Appendices A, B and C). DSMB members will be given the opportunity to provide input on the frequency of subsequent DSMB meetings as well as on presentation specifications and the logistics of the interactions between the DSMB, CTI and Edimer.

Attendees: DSMB Members
CTI Representative(s)
Project Study Manager
Project Statistician
Edimer Representatives
Medical Monitor/Vice President, Clinical Development
Senior Director, Clinical and Regulatory Operations

Documents needed: Final protocol (Appendix A)
Case Report Forms (Appendix B)
Table shells to be issued to the DSMB (Appendix C)
Draft DSMB Charter

Output: Comments on table shells and operating guidelines
Comments on communication and unexpected updates

4.2 Scheduled Meetings

Subsequent meetings of the DSMB will be scheduled as outlined in Section 6 and at the discretion of the DSMB. Each meeting may consist of an open session and a closed session and may be structured according to sections 4.2.1 to 4.2.3.

4.2.1 Open Session: General Update

Attendees: DSMB Members
CTI Representatives:
Project Study Manager
Project Statistician
Edimer Representatives
Medical Monitor/Vice President, Clinical Development
Senior Director, Clinical and Regulatory Operations
Principal Investigators
PK Consultant (as needed)

Documents to be provided: DSMB Reports (see Appendix C)

Output: Minutes of Open DSMB Meeting

4.2.2 Closed Session

Attendees: DSMB Members
Output: DSMB Recommendation(s)

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4.2.3 Unscheduled Meetings

In the case of any unexpected safety problems the study Medical Monitor or Principal Investigator will notify the Sponsor and the DSMB who will have the option to call an unscheduled DSMB meeting.

5. COMMUNICATION

5.1 Reports

Reports will include data as outlined in Appendix C. The reports will be prepared by CTI and provided to the DSMB prior to the meeting. Each report will include an executive summary of key findings.

5.2 DSMB Minutes

A representative from the CRO (CTI) will prepare minutes of the open sessions.

5.3 DSMB Recommendation

At each meeting, the DSMB will recommend whether the study should continue, stop permanently or stop temporarily and be modified. The Chair of the DSMB will notify the Sponsor of the DSMB recommendations with a written communication within 24 hours of the meeting. The DSMB may request participation of an additional individual with specific expertise, should the need arise.

5.4 Sponsor Decision

If the DSMB recommends stopping the trial, individuals identified by the Sponsor, who have the clinical, biostatistical, regulatory, and business expertise needed to make critical decisions for the Sponsor, will meet to review the Reports. They will review the DSMB recommendation, seek input from regulatory agencies and then make a decision to accept or disregard the recommendation to stop the trial. If the Sponsor decides to accept the recommendation, the clinical trial will be stopped; if the Sponsor decides to disregard the recommendation, the clinical trial will continue. The Sponsor will assure that confidentiality of the data will be maintained.

If the DSMB recommends that the clinical trial be terminated, but the Sponsor decides to continue the clinical trial, the Sponsor will provide the DSMB a written explanation of the decision within 14 days. The Sponsor will notify the regulatory authorities of the DSMB recommendation and the Sponsor's decision. The DSMB recommendation and the

Sponsor's decision will also be disclosed in the published report of the primary study findings.

If the DSMB and the Sponsor agree to stop the trial, the Sponsor will inform all regulatory agencies of the decision prior to notifying the investigational centers. Public disclosure of the decision to stop the trial is at the Sponsor's discretion. The DSMB will not make any public announcements before the Sponsor is ready for public disclosure.

5.5 Submission of Study Accrual and SAEs

As each SAE occurs, CTI will forward to the members of the DSMB copies of accrual numbers and incidence of SAEs along with the available details and clinical scenario of the new SAE in a timely manner.

5.6 DSMB Additional Data Requests

The Chair of the DSMB, after the approval of all other members, may request additional data from CTI. CTI will notify the Sponsor of the request, but without providing more detail than necessary concerning the nature the data requested.

If, based on the additional data, the DSMB feels that there is a need for an unscheduled formal analysis and meeting, the Chair of the DSMB will notify the Sponsor's Study Medical Monitor and Medical Director. All data requests together with justification will be documented and supplied to the Sponsor at the end of the study.

6. TIMETABLE

Scheduled Meetings		
Meeting Type	**Timing**	**Output**
Organizational Meeting and Review of Cohort 1 Data from Adult Study	Protocol final and prior to study initiation	Final approved DSMB Charter
Cohort 1 Review (and Review of Cohort 2 Data from Adult Study)	Approximately 2 weeks after all Cohort 1 Dosing Complete	Minutes and Recommendation
Cohort 2 Review	Approximately 2 weeks after all Cohort 2 Dosing Complete	Minutes and Recommendation
Every Six Months	Meetings will be held every six months at minimum in the event that no other scheduled meetings are required	Minutes and Recommendation
Study Completion	6 to 8 weeks after Month 6 of Life Visit for last subject of Cohort 2	Minutes and Final DSMB Report
As Needed/Unscheduled Meetings		
As needed based upon real time review of subject safety data	As safety data becomes available	Minutes and Recommendation
Suspension of dosing in any cohort	As soon as possible after dosing is suspended and required data are available	Minutes and Recommendation
Study stopped for any reason	As soon as possible after study is stopped and when required data are available	Minutes and Recommendation
Protocol amendment review	When protocol amendments become available for review	Minutes and Recommendation

APPENDIX A: Protocol and Informed Consent Form

To be inserted

APPENDIX B: Case Report Forms

To be inserted

APPENDIX C: DSMB Report Templates

The following reports will be provided to the DSMB:

1. Demographics and Disposition
2. Physical Exam results
3. Vital signs
4. Adverse events
5. Concomitant therapy
6. Infusion site reactions
7. Safety data/laboratory results
8. PK data
9. Pharmacodynamic/efficacy data
10. Protocol deviations
11. Serious Adverse Event case report

Proposed table shells for these reports will be presented to the DSMB at the Organizational Meeting.

APPENDIX D: Contact Lists

DSMB Contact Information		
Name	**Role**	**Contact Information**
Michael J. Corwin, MD	DSMB Chairperson	Care-Safe LLC 24 Crescent St., Suite 305 Waltham, MA 02453 Phone: (617) 966-7777 Email: mjcorwin@care-safe.com
Stephen Pelton, MD	DSMB Member	49 Rawson Road Brookline, MA 02445 Phone: (617) 414-7407 Email: spelton@bu.edu
John Rogus	DSMB Member	458 Foster St North Andover, MA 01845 Phone: (508) 847-9451 Email: jjrogus@gmail.com
Christian Poets	DSMB Member	Prof. Christian F. Poets, MD Dept. of Neonatology, Tübingen University Hospital Calwerstr. 7, 72076 Tübingen Phone: -49 7071 298 4715 Email: christian-f.poets@med.uni-tuebingen.de

Other Study Contacts		
Name	**Role**	**Contact Information**
Kenneth Huttner, MD PhD	Sponsor Senior Vice President, Clinical Development and Study Medical Monitor	Edimer Pharmaceuticals 55 Cambridge Parkway Suite 102W Cambridge MA 02142 Phone: (617) 758-4300 Email: khuttner@edimerpharma.com
Ramsey Johnson	Sponsor Senior Director, Clinical and Regulatory Operations	Edimer Pharmaceuticals 55 Cambridge Parkway Suite 102W Cambridge MA 02142 Phone: (617) 758-4305 Email: rjohnson@edimerpharma.com
TBD	Principal Investigator	TBD
David McCollum, MS Associate Director, Biostatistics	CRO DSMB Statistician	CTI Clinical Trial and Consulting Services 10123 Alliance Road Cincinnati, OH 45242 Phone: (513) 619-1846 Fax: (513) 598-6909 Email: dmccollum@ctifacts.com
Sibylle Lindsey	CRO Study Manager	CTI Clinical Trial and Consulting Services 10123 Alliance Road Cincinnati, OH 45242 Phone: (513) 619-1893 Fax: (513) 598-6909 Email: slindsey@ctifacts.com
Dennis Fisher, MD	PK Consultant	P< (The “P Less Than” Company) 218 Castenada Avenue San Francisco, CA 94116 Phone: (866) 753-7784 Fax: (866) 753-7784 Mobile: (415) 307-4791 Email: fisher@plessthan.com> www.PLessThan.com

DSMB Meeting Minutes
Cohort 1: First Subject Review
30 Oct 2013

Protocol ECP-002

DSMB Meeting – Cohort 1: First Subject Review

October 30, 2013, 8:30 A.M – 9:30 A.M ET

Attendees:
DSMB Members: Michael Corwin (Chair), Stephen Pelton, John Rogus, Christian Poets
Edimer: Ramsey Johnson, Ken Huttner, Lori Correia
University Hospital Erlangen Nurnberg: Holm Schneider (PI)
CTI: Tom Winrod, Dave McCollum, Cynthia Fairbairn

Listings provided to the DSMB members prior to the meeting:
CTI: Subject disposition, protocol deviations, demographic characteristics and eligibility criteria, study drug administration, medical questionnaire, medical history, concomitant medications, adverse events, lab results, vital signs, and physical exam abnormalities.

1. **Overview**

- Format of meeting was discussed.
  - During the open session, an update on study progress will be provided. Additionally, DSMB members will provide feedback on whether they have all necessary information. Clarification on study events will be provided if needed.
  - In the closed session, the DSMB members will discuss details of the study events and determine if it is acceptable to advance with the study or if more information is needed.
- Site update was discussed by R. Johnson:
  - US sites
    - There are two active sites in the US with the third and final site scheduled for an SIV on 15Nov2013.
  - EU sites
    - In Germany, the Erlangen site is currently active.
    - The UK site has received Regulatory Authority approval and the Ethics Committee approval is in process.
    - The site in France has submitted to their Ethics Committee and Regulatory Authority.
- Potential subjects were discussed in detail:
  - The first subject was enrolled at Erlangen.
  - At this time, there is a baby due on 09Nov2013 that is being tracked. The mother is a carrier and expecting a boy; but, the baby has not been confirmed to be XLHED affected. If affected, the mother has indicated strong interest in participation in the study and enrollment will occur at the University of California, San Francisco.

- Additional, pregnancies are being followed with 2-3 due in Jan2014 and a few in Feb and Apr2014.

- If the DSMB determines that it is acceptable to proceed with the study, then the next subject will be potentially enrolled during the second week of Nov2013.
- The DSMB members discussed the formatting of the listings. Formatting of the listings is acceptable. It is preferred that the listings be provided earlier to allow 4-5 days for the members to review. C. Poet requested that the listings be provided as a PDF attached to an email.
- 1 subject was enrolled at University Hospital Erlangen Nurnberg and has completed dosing and followed through the Day 28 visit.
- Concomitant medications were discussed.
  - Per DSMB members, it would be preferred to know the drug indication and the amount given including mg/kg.
- Protocol deviation discussed in more detail:
  - Baseline weight was to be used per the protocol for drug administration. The PI used birth weight for calculating study drug dose instead of baseline weight.
  - Given that the child was born at the hospital in Erlangen Dr. Schneider elected to use the birth weight given the reliability of the data. In most other cases the birth will have taken place at another hospital and it will be more accurate to use weight on study admission as baseline. Clarification to protocol regarding the weight to be used for dose calculation will be given.

2. **PI Dr. Schneider (University Hospital Erlangen Nurnberg) provided input on dosing of first subject 3063-001**

- Protocol worked well.
- From the experience of performing the baseline assessments, Dr. Schneider suggested that it would be best to perform these assessments over the course of several days rather than all in one day.
  - The infant was delivered on 15Sep2013 and transferred to the ward on 17Sep2013 at which time all baseline events were performed.
  - Spreading the baseline procedures over 2-3 days will allow the infant to maintain a more normal feeding and sleeping schedule.
- Summary of infant's disposition:
  - Infant's body temperature increased while under heat lamp for initial examination.
  - Infant's breastfeeding and behavior was normal.
  - Weight gain was normal
- Adverse event overview:
  - Hyponatremia and hypoalbuminemia occurred and both resolved without intervention
  - Redness at the biopsy site occurred with the third biopsy. This was a mild inflammatory reaction that disappeared without treatment after 3 days.
- Concomitant medications discussed:

- An IV infusion of normal saline was administered at a low infusion rate to ensure that the peripherally-insert long line remained open.
- The baseline procedures attempted in a single day overstimulated the neonate. Thus, multiple doses of Midazolam were administered to calm the infant for the microscopy, biopsy, x-ray and line placement.
- Vitamin D with fluoride is administered as routine care to neonates after 10th day of life.

Follow-up needed: Sedation for procedures is not indicated in the protocol and should be clarified with the sites.

- No clinically significant changes were noted in the child's vital signs.
- Assessments:
  - Immediately after birth, the skin was noted to be shiny, dry and thin. The skin was very healthy appearing on day 21.
  - Child was born with no eyebrows, eyelashes or hair. Between Day 12 and 14, the mother called PI over and reported that eyelashes were developing as well as hair on the head. This will be compared to infant pictures of affected uncles when available.
  - During the second thermoregulation assessment, which occurred on day 21, the infant coped with the increased temperature longer and remained in the incubator for 13-14 minutes longer.

3. Closed Session and Summary of Meeting

- On 30Oct2013 after the conclusion of the closed session the DSMB Chair send an email to R. Johnson and K. Huttner in which he indicated that the committee discussed the observed adverse events of hyponatremia and hypoalbuminemia on study day 21, and felt that such fluctuations in sodium and albumin were not uncommon in young infants. Based on the relatively rapid return to normal without the need for treatment, these were considered to be of only mild to moderate clinical importance.
- The DSMB did request that if similar events are observed in subsequent subject, that additional evaluations be performed to help better understand potential explanations for these fluctuations in lab values.
- The DSMB also noted that the need for sedation for the performance of the study biopsies was not anticipated in the protocol and that this issue needs to be addressed in both the protocol and the study consent form. A letter of clarification is being sent to the sites to clarify that the use of sedation is not recommended for any of the proposed study procedures.

DSMB Meeting Minutes
Cohort 1 Review
22 Apr 2014

From: **Michael Corwin** mjcelibri@gmail.com
Subject: DSMB closed session
Date: April 22, 2014 at 10:06 AM
To: Ramsey Johnson ramsey@edimerpharma.com, Kenneth Huttner ken@edimerpharma.com, John Rogus jjrogus@gmail.com, Stephen Pelton spelton@bu.edu, Christian Poets christian-f.poets@med.uni-tuebingen.de

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Ramsey and Ken

April 22, 2014: Summary of Closed DSMB Session

The committee reviewed the data from all three cohort 1 subjects and felt there were no significant safety issues observed that would prevent moving on to cohort 2 dosing.

It was noted in the PK report that there were values for the third subject that suggested there may have been a mix-up in the samples. PK analyses were performed with a re-ordering of the samples, and those analyses suggested that drug levels in the neonates were sufficiently consistent with adult values from prior studies that advancing to the next dosing cohort could be permitted. However, the DSMB is requesting that the PK report include a discussion of alternative “worst-case” scenarios for the potentially mixed-up PK samples, to reassure that alternative analyses would also provide results that were sufficiently similar to adult values to move on to the next dosing cohort.

We also suggest that all aspects of the quality control of obtaining and analyzing PK samples be reviewed.

Thanks

Mike

DSMB Meeting Minutes
Cohort 2: First Review
3 Feb 2015

From: **Michael Corwin** mjcelibri@gmail.com
Subject: DSMB recommendations
Date: February 3, 2015 at 4:02 PM
To: Neil Kirby neil@edimerpharma.com, Ramsey Johnson ramsey@edimerpharma.com, Kenneth Huttner ken@edimerpharma.com

MC

Ken

The DSMB reviewed the data from the fifth subject in cohort 2, along with the updated data from the three subjects in cohort 1, and the first four subjects in cohort 2, and did not observe significant safety concerns.

The DSMB also reviewed the PK data from the first seven subjects enrolled, as well as a summary of the levels of exposure in animals that relate to safety and efficacy. It was noted that there was large variability among infants in the PK parameters, as well as challenges in the interpretation of the animal PK data. Therefore the DSMB feels that it needs a second independent review of the data by an expert in pharmacokinetics in the drug development setting prior to making a judgment regarding the most appropriate dosing for cohort 3.

Thanks

Mike

DSMB Meeting Minutes
Cohort 2 Review
10 Feb 2015

CARE-SAFE

February 10, 2015

Ramsey Johnson, MSM
Sr. Director, Clinical & Regulatory Operations
Edimer Pharmaceuticals
55 Cambridge Parkway
Suite 102W
Cambridge MA 02142

Dear Mr. Johnson:

The DSMB met by phone on February 10, 2015 to discuss the proposal by Edimer to use a dose of 30mg/kg in the next study cohort, a three-fold increase from the prior cohort.

This discussion included the four DSMB members plus Dr. William Kramer, an expert in clinical pharmacology, pharmacokinetics and pharmacodynamics.

Although the DSMB is reassured by the lack of safety concerns to date, we recommend that the dose for the next cohort be increased to 20mg/kg, rather than 30mg/kg. We also request that PK data be provided to the DSMB on a subject-by-subject basis as soon as possible, although not necessarily at the time of the initial safety review to approve dosing of the next subject. In addition, since we understand that Edimer will be investigating a possible site-based problem with assessing PK parameters, the DSMB would like to see the results of that investigation as soon as it becomes available.

We believe this more conservative approach is justified for several reasons:

1) Newborn infants are a vulnerable population with the potential to have difficult to predict drug metabolism.
2) The number of infants assessed to date is still quite low, and the site-based PK issues mentioned above further limit the assessment of drug exposure. Together these factors suggest a need to be conservative in dose escalation.
3) The suggested doubling of the dose to 20mg/kg represents an increase in dose with a reasonable potential to be efficacious, based on the animal data.

Sincerely,

Michael J. Corwin, MD

Chair, DSMB

Appendix 16.5- SAE Narratives

Case Number	Patient Number
ECP2X20160001	3005-001
ECP2X20140001	3063-001
ECP2X20140002	3063-002
ECP2X20150001	3063-003
ECP2X20150002	3063-003
ECP2X20150004	3064-002

ECP-002 Neonate Study SAE Listing

For the Period 01-Jan-2000 Through 01-Jan-2999

Case Num	Study Protocol ID	Patient Subject #	Case Narrative
ECP2 X20160001	ECP-002	3005-001	This clinical trial case concerns a 10 week-old, Caucasian male, subject 3005-001. On 30-Jul-2014, the subject was enrolled in ECP-002, Ph 2 OL, dose escalation study for safety, efficacy of EDI200, an EDA-A1 replacement protein, to infants with x-linked hypohidrotic-ectodermal dysplasia (XLHED), and began EDI200 on 04-Aug-2014. Medical history included congenital ectodermal dysplasia, anemia, elevated chloride, low hemoglobin and hematocrit, and elevated neutrophils, monocytes, lymphocytes, and eosinophils. Concomitant medications were Uvesterol (ascorbic acid, ergocalciferol, retinol, tocopherol), Ferrostrane (sodium feredetate), and folic acid. On 04-Aug-2014, the subject received the first dose of study drug, 35 mg intravenously (IV). He received the second dose of 39.0 mg IV on 08-Aug-2014, third dose of 39.3 mg IV on 11-Aug-2014, fourth dose of 40.6 mg IV on 14-Aug-2014 and the fifth dose of 47.1 mg IV on 18-Aug-2014. On 21-Sep-2014, 33 days after taking the last dose of study product, the subject developed pyelonephritis (Intensity; mild) and was hospitalized for 3 days. He was treated with Oroken (cefixime) antibiotic. The event was considered resolved on 24-Sep-2014 and the subject was discharged from the hospital. The investigator reported the event of pyelonephritis was unlikely related to study the study drug. Additional information has been requested.
ECP2X20140001	ECP-002	3063-001	This clinical trial case concerns a 4 months old Caucasian male subject 3063-001, date of birth15-Sep-2013. On

ECP-002 Neonate Study SAE Listing

For the Period 01-Jan-2000 Through 01-Jan-2999

Case Num	Study Protocol ID	Patient Subject #	Case Narrative
			16-Sep-2013, the subject was enrolled in ECP-002, Ph 2 OL, dose escalation study for safety, efficacy of EDI200, an EDA-A1 replacement protein, to male infants with X-linked hypohidrotic ectodermal dysplasia (XLHED), and began EDI200 on 18-Sep-2013. Concomitant medications included Zymafluor D (cholecalciferol, sodium fluoride). There was no additional relevant medical history. The subject received the initial dose of study drug EDI200 on 18-Sep-2013 with subsequent doses on 22-Sep-2013, 25-Sep-2013, 29-Sep-2013 with the final dose on 02-Oct-2013 for a total of 5 doses. On 11-Feb-2014, 131 days after taking his last dose of study product, the subject was hospitalization for respiratory syncytial virus (RSV) infection (intensity; severe). For 3 days he had a cold with a maximum temperature of 38.8 degree celsius (C). He had a dry cough and his breathing had been difficult since the day of admission. Physical examination revealed that he was in stable condition, good nutritional status, and unremarkable psychomotor development, pale, rosy skin with no eyelashes or eyebrows. He had free moving musculoskeletal system, normal rhythmic heart sounds, aggravated breath sounds bilaterally, benign fine rales, slight tachypnea, prolonged expiration, abdomen was soft with no hepatosplenomegaly and normal bowel sounds. The remainder of the internal and neurologic examination was unremarkable. Vital signs revealed temperature 38 degree C, pulse 100 per minute, blood pressure 98/67 mmHg and oxygen saturation 100%. Laboratory tests on 11-Feb-2014 revealed respiratory syncytial virus test (RSV) was positive, blood gas pH 7.4, pCO2 38.3 mmHg, pO2 47.6

ECP-002 Neonate Study SAE Listing

For the Period 01-Jan-2000 Through 01-Jan-2999

Case Num	Study Protocol ID	Patient Subject #	Case Narrative
			mmHg, glucose 106 mg/dl, HCO3 23.2 mmol/l (normal ranges were not provided) and remaining electrolytes were unremarkable. Treatment included inhalations of salbutamol, epinephrine, and 3% saline for mucolysis. He was supported with glucose and electrolyte infusions. During the first nights he required 2 liters (L) of oxygen. Under these measures his condition stabilized quickly. His inhalations were tapered and he was discharged in good condition on 14-Feb-2014 and the event of RSV infection was considered resolved. Medications on discharge included normal saline (NaCl) 0.9% inhalations 3 times a day with Pari Boy. No action was taken with study medication. The investigator reported that the event of RSV infection was not related to study medication. Update 07-Apr-2014; additional information received from site, updated AE page, no new SAE information.
ECP2X20140002	ECP-002	3063-002	This clinical trial case concerns a 3 week old Caucasian female subject 3063-002. On 29-Oct-2014, the subject was enrolled in ECP-002, Ph 2 OL, dose escalation study for safety, efficacy of EDI200, an EDA-A1 replacement protein to infants with x-linked hypohidrotic-ectodermal dysplasia (XLHED), and began EDI200 on 02-Nov-2014. Medical history included ectodysplasin A (EDA) gene mutation, oligodontia and hypoalbuminemia. Concomitant medications were glucose, midazolam, and Zymafluor D (cholecalciferol, sodium fluoride). On 02-Nov-2014, the subject received the first dose of study drug, 30 mg intravenously (IV). On 05-Nov-2014, the subject received the second dose of study drug, 33 mg IV. On 09-Nov-2014, the subject received the third dose of study

ECP-002 Neonate Study SAE Listing

For the Period 01-Jan-2000 Through 01-Jan-2999

Case Num	Study Protocol ID	Patient Subject #	Case Narrative
			drug, 33 mg IV. From 09-Nov-2014 through 12-Nov2014 the subject was out of the hospital. On 09-Nov-2014, the subject received the third dose of study drug, 33 mg IV. On 12-Nov-2014, two and a half days after the third dose of study drug, the subject was seen for her planned re-admission visit for her continued treatment with the study drug. Upon admission, she was found to have a febrile upper respiratory infection (intensity, moderate per investigator and severe per CTCAE grading). She had a rectal temperature of 37.6 degrees Celsius. Laboratory tests on 12-Nov-2014 revealed leucocytes (white blood cell count) 18730 ul (NR: 8360-14420), pO2 36 mmHg (NR: 36-44), C-reactive protein (CRP) 45.8 mg/l (NR: <5) and monocytes 2600 ul (NR: 420-1210). A nasal swab for respiratory syncytial virus was negative. The babys father had been fighting an upper respiratory infection for more than a week and was the likely cause of the infection. The baby was not seriously ill but the development of a fever suggested the need for intravenous antibiotics for seven days. The subject was treated with piperacillin 0.3 g IV twice daily (BID) and tobramycin 15 mg IV once daily (QD). On 14-Nov-2014, the subject received the fourth dose of study drug, 33 mg IV and on 16-Nov-2014, the subject received the fifth and last dose of study drug, 33 mg IV. On 18-Nov-2014, piperacillin and tobramycin were discontinued. The subject was reported to have recovered from the event on 18-Nov-2014. All symptoms resolved in a prompt fashion. The action taken with regard to study medication was no

ECP-002 Neonate Study SAE Listing

For the Period 01-Jan-2000 Through 01-Jan-2999

Case Num	Study Protocol ID	Patient Subject #	Case Narrative
			change. She continued on study drug with no reactions noted. The investigator reported that the event of febrile upper respiratory infection was medically significant and was unlikely related to study drug. Additional information received from the site on 20-Nov-2014 was processed with initial case. Update 02-Dec-2014; Additional information received from the site on 26-Nov-2014 and 02-Dec-2014 included additional information around the diagnosis of the event and relevant labs.
ECP2X20150001	ECP-002	3063-003	This clinical trial case concerns a nine week old Caucasian male subject 3063-003. On 14-Nov-2014, the subject was enrolled in ECP-002, Ph 2 OL, dose escalation study for safety, efficacy of EDI200, an EDA-A1 replacement protein to infants with x-linked hypohidrotic-ectodermal dysplasia (XLHED), and began EDI200 on 26-Nov-2014. Medical history included hypohidrotic ectodermal dysplasia (HED), hypoalbuminemia, anemia and oral candida infection. Concomitant medications were sodium fluoride. On 26-Nov-2014, the subject received the first dose of study drug, 28 mg intravenously (IV). On 01-Dec-2014, the subject received the second dose of study drug, 28 mg IV. On 04-Dec-2014, 07-Dec-2014 and 10-Dec-2014 the subject received the third, fourth and fifth dose of study drug 32 mg IV.

ECP-002 Neonate Study SAE Listing

For the Period 01-Jan-2000 Through 01-Jan-2999

Case Num	Study Protocol ID	Patient Subject #	Case Narrative
			The subject has been treated in the outpatient pediatric genetics clinic for HED. On 25-Jan-2015, he was taken to the emergency room for difficulty breathing and acute respiratory problems. The infant was admitted to the hospital (neonatal intensive care due to no pediatric bed availability) with generalized dyspnea and bronchiolitis (intensity; severe) and he was agitated and irritable. His oxygen saturation was less than (<) 91% at rest and on auscultation he had fine rales primarily in the right anterior region with notes of diffuse bronchospasm. He had diffuse secretions in the upper respiratory tract and a barking cough. A nasogastric tube was inserted due to sucking difficulty to ensure adequate dietary intake. Laboratory tests revealed negative inflammatory markers and a chest x-ray revealed the presence of indistinct left inferior retrocardiac thickening possibly suggestive of the vascular hilum, which should be confirmed by clinical data. No additional focal parenchymal changes were visible, no bilateral pleural effusions were noted and a normal heart shadow was seen; thus antibiotic treatment was not administered. The infant was placed in a crib with free flow oxygen (FiO2) maximum 0.4 and humidification at 85% and a trial with aerosol adrenaline which decreased the need for FiO2 25%. Later that day on 25-Jan-2015 he was transferred to the pediatric floor. Vital signs revealed oxygen saturation on room air 100%, heart rate 140 beats per minute (bpm) and apyretic. Physical examination revealed in general good condition. Chest auscultation revealed diffuse fine rales, prolonged expiration, intercostal retractions and polypnea. Treatment included continued aerosol with adrenaline in 3% hypertonic solution every five hours from 25-Jan-2015 through 26-Jan-2015. His respiratory condition improved and he was treated with aerosol, without adrenaline, with 3% hypertonic solution

ECP-002 Neonate Study SAE Listing

For the Period 01-Jan-2000 Through 01-Jan-2999

Case Num	Study Protocol ID	Patient Subject #	Case Narrative
			every five hours on 26-Jan-2015 and then every six hours on 27-Jan-2015. On 27-Jan-2015, he restarted normal eating by mouth therefore the nasogastric tube was removed. He was discharged from the hospital on 27-Jan-2015 in good condition, eupneic and apyretic. Oxygen saturations were 100% on room air and his breath sounds revealed no harsh vesicular or abnormal sounds. He was to continue aerosol therapy with 3% hypertonic solution, 3 ml, three times a day for three to four days and frequent nasal irrigations. He recovered from the event of bronchiolitis on 27-Jan-2015. The action taken with regard to study medication was no change. The investigator reported the event of bronchiolitis was not related to study medication. Update 31-Mar-2015; additional information received from the site confirmed the event stop date.
ECP2X20150002	ECP-002	3063-003	This clinical trial case concerns a 4 ½ month old Caucasian male subject 3063-003. On 14-Nov-2014, the subject was enrolled in ECP-002, Ph 2 OL, dose escalation study for safety, efficacy of EDI200, an EDA-A1 replacement protein to infants with x-linked hypohidrotic-ectodermal dysplasia (XLHED), and began EDI200 on 26-Nov-2014. Medical history included hypohidrotic ectodermal dysplasia (HED), hypoalbuminemia, anemia and oral candida infection. Concomitant medications were sodium fluoride and

ECP-002 Neonate Study SAE Listing

For the Period 01-Jan-2000 Through 01-Jan-2999

Case Num	Study Protocol ID	Patient Subject #	Case Narrative
			colecalciferol. On 26-Nov-2014, the subject received the first dose of study drug, 28 mg intravenously (IV). On 01-Dec-2014, the subject received the second dose of study drug, 28 mg IV. On 04-Dec-2014, 07-Dec-2014 and 10-Dec-2014 the subject received the third, fourth and fifth dose of study drug 32 mg IV. The subject has been treated in the outpatient pediatric genetics clinic for HED. On 25-Jan-2015, the subject was hospitalized and treated for bronchiolitis. He recovered from the event and was discharged on 27-Jan-2015. (ECP2X20150001). On 07-Apr-2015, the infant subject had a sudden onset of fever. On 09-Apr-2015, during a scheduled follow up at the outpatient clinic, he was noted to have persistent fever associated with acute mild otitis of the left ear and pharyngitis. The infant was prescribed treatment with amoxicillin. Starting on 10-Apr-2015, he showed lack of appetite and overnight dyspnea. He was taken to the emergency room, and due to the evidence of dyspnea and desaturation, he was administered aerosol with salbutamol and oxygen therapy, with partial benefit. The infant was admitted to the hospital, on 11-Apr-2015, for bronchopneumonia (intensity; severe). Laboratory blood test results were normal with a negative inflammatory markers. Chest x-ray results showed dyshomogeneous upper right perihilar lung thickening. Lung opacities were evident above the left diaphragmatic space. The upper mediastinum appeared enlarged and there was no active effusions. Upon physical examination, the infant was noted to be in good general condition. His oxygen saturation was 93% before the

ECP-002 Neonate Study SAE Listing

For the Period 01-Jan-2000 Through 01-Jan-2999

Case Num	Study Protocol ID	Patient Subject #	Case Narrative
			aerosol treatment and 98% following the aerosol treatment. His respiration rate was 48 breaths per minute, oropharynx pink and clean, tympanic membranes normal and heart and abdominal findings within normal limits. On chest auscultation, normal vesicular breathing associated with bilateral basal crackles was noted. The infant was treated with ongoing amoxicillin and clavulanic acid, which had been initiated on 10-Apr-2015. Due to the bronchospasms and oxygen saturation levels below 92% and 87% during sleep, he was treated with oxygen on demand, mostly during sleep, and aerosol therapy with salbutamol and ipratropium bromide. Additional treatment included steroid therapy with betamethasone. On 15-Apr-2015, the 5th post hospitalization day, the results of the blood culture test that were obtained on admission came back positive for Serratia marcescens, resistant to amoxicillin and clavulanic acid; therefore ceftazidime was started and continued through 21-Apr-2015. The infant showed gradual improvement and on the 8th post hospitalization day, the steroid therapy was interrupted and bronchodilator treatment was reduced. On 21-Apr-2015, the infant recovered from the event of bronchopneumonia and he was discharged from the hospital, on the following day, 22-Apr-2015. His weight at discharge was 6.42 kg, compared to 6.3 kg on admission. There was no action taken with study medication. The investigator reported the event of bronchopneumonia was unlikely related to study medication. Translation received on 25-May-2015 and 26-May-2015 processed with initial case.

ECP-002 Neonate Study SAE Listing

For the Period 01-Jan-2000 Through 01-Jan-2999

Case Num	Study Protocol ID	Patient Subject #	Case Narrative
			Update 10-Jun-2015: Follow up information received on 10-Jun-2015 from the site included confirmation that the event term should remain as reported and confirmation of the hospital discharge date. Update 25-Jun-2015: Follow up information received on 25-Jun-2015 from the site included confirmation that culture results from subject's primary care physician have not yet been received. No additional information was provided. Update 29-Oct-2015: Follow up information received from the site on 21-Oct-2015 included confirmation of blood culture results. Update 22-Dec-2015: The event term was compressed per reconciliation from bronchopneumonia with bacteremia to bronchopneumonia. The case has been updated accordingly. Companion case: (ECP2X20150001)
ECP2X20150004	ECP-002	3064-002	This clinical trial case concerns an 11 week-old, Caucasian male, subject 3064-002. On 06-Apr-2015, the subject was enrolled in ECP-002, Ph 2 OL, dose escalation study for safety, efficacy of EDI200, an EDA-A1 replacement protein, to infants with x-linked hypohidrotic-ectodermal dysplasia (XLHED), and began EDI200 on 09-Apr-2015. Medical history included x-linked hypohidrotic ectodermal dysplasia (XLHED), crumpled and over-folded ears, sparse brows, underdeveloped alveolar ridges (patchy), dry skin, sparse eyelashes, nasal congestion, peeling skin, low creatinine, high alkaline phosphatase, high hemoglobin, and high hematocrit.

ECP-002 Neonate Study SAE Listing

For the Period 01-Jan-2000 Through 01-Jan-2999

Case Num	Study Protocol ID	Patient Subject #	Case Narrative
			Concomitant medications were Saline Nasal drops (sodium chloride), Hydromol (sodium pidolate), Diprobase cream (paraffin, liquid and white soft paraffin), Diphtheria vaccine, Tetanus vaccine, Pertussis vaccine, and Haemophilus influenza Type B vaccine. On 09-Apr-2015, the subject received the first dose of study drug, 63.5 mg intravenously (IV). On 13-Apr-2015 and 16-Apr-2015, the subject received the second and third dose of study drug, 63.5 mg IV. On 20-Apr-2015 and 23-Apr-2015 the subject received the fourth and fifth dose of study drug 71.0 mg IV. On 20-Jun-2015, 57 days after taking the last dose of study product, the subject experienced a chest Infection (Intensity; severe). On 30-Jul-2015, he was subsequently hospitalized at an out of town facility. The chest x-ray report and laboratory results were reported as unavailable. The subject was treated with a combination of unspecified IV and oral antibiotics for a total of 10 days. The subject was discharged from the hospital on 06-Jul-2015. On 07-Jul-2015, the subject was reported to have recovered from the event of chest infection. There was no action taken with study medication. The investigator reported the event of chest infection as not related to study medication. Update 22-Dec-2015. Follow up information received from the site on 18-Dec-2015 included confirmation that the chest x-ray report, blood test results, dates of antibiotic treatment and the discharge summary remain unavailable, despite several request of additional information from an outside source where subject was hospitalized.

ECP-002 Neonate Study SAE Listing

For the Period 01-Jan-2000 Through 01-Jan-2999

Case Num	Study Protocol ID	Patient Subject #	Case Narrative

Total Row Count: 6

Total Cases: 6

Appendix 16.6- Pharmacokinetic Report

Edimer Pharma

Sponsor Signatory Signature Page

Edimer Study ECP-002:
Pharmacokinetic Analysis for Cohorts 1, 2 and 3

Development Phase: 2

I have read this report and confirm that, to the best of my knowledge, the pharmacokinetic analysis was conducted as described.

Name of Sponsor Signatory:

Title of Sponsor Signatory:

Sponsor: Edimer Pharmaceuticals
55 Cambridge Parkway, Suite 102W
Cambridge, MA 02142

Signature: 

Date: 12th May 2016

Data Analyst Signature Page

Edimer Study ECP-002: Pharmacokinetic Analysis for Cohorts 1, 2 and 3

I have read this report and confirm that, to the best of my knowledge, the pharmacokinetic analysis was conducted as described.

Name of Data Analyst: Dennis M. Fisher, M.D.

Affiliation: The "P Less Than" Company
218 Castenada Avenue
San Francisco, CA 94116

Telephone, fax: (866) 753-7784
Email: fisher@plessthan.com

Signature of Data Analyst: 

Date: 11 May 2016

Title:	**Edimer Study ECP-002:** **Pharmacokinetic Analysis for Cohorts 1, 2 and 3**

Phase: 2

Compound Names: EDI200

Description: The report summarizes a population pharmacokinetic analysis of EDI200.

Subject: EDI200 pharmacokinetics; mixed effects analysis

Author: Fisher, Dennis M.

This study was performed in compliance with Good Clinical Practices, including the archiving of essential documents.

Introduction

Ten neonates have been dosed in Edimer Study ECP-002, each having received five doses of 3 mg/kg EDI1200 (N = 3), 10 mg/kg EDI1200 (N = 5), or 20 mg/kg EDI1200 (N = 2). Samples were obtained before the first dose (Day 0), 15 minutes, 3, 8, 24, and 48 hours after the first dose, before the fifth dose (Day 14), 15 minutes, and 3, 18, 48, and 168 hours after the fifth dose, and at Month 2 and Month 6.

Data Assembly

Dosing history, demographic and concentration data were received from Edimer as Excel spreadsheets. The dataset was constructed using R (r-project.org, version 3.2.2).

Seventeen (17) samples were reported as having a concentration of zero (limit of quantification was 0.0391 µg/ml). Of these 17 samples, 10 were pre-dose samples, one was a sample obtained at Month 2, and six were samples obtained at Month 6. For the subject whose sample was BQL (less than the assay's lower limit of quantification) at Month 2, the sample at Month 6 was reported to have a concentration of 0.0458 µg/ml, only slightly > assay LOQ. Serum concentration data and doses for each subject are shown in **Figure 1** and **Figure 2**.

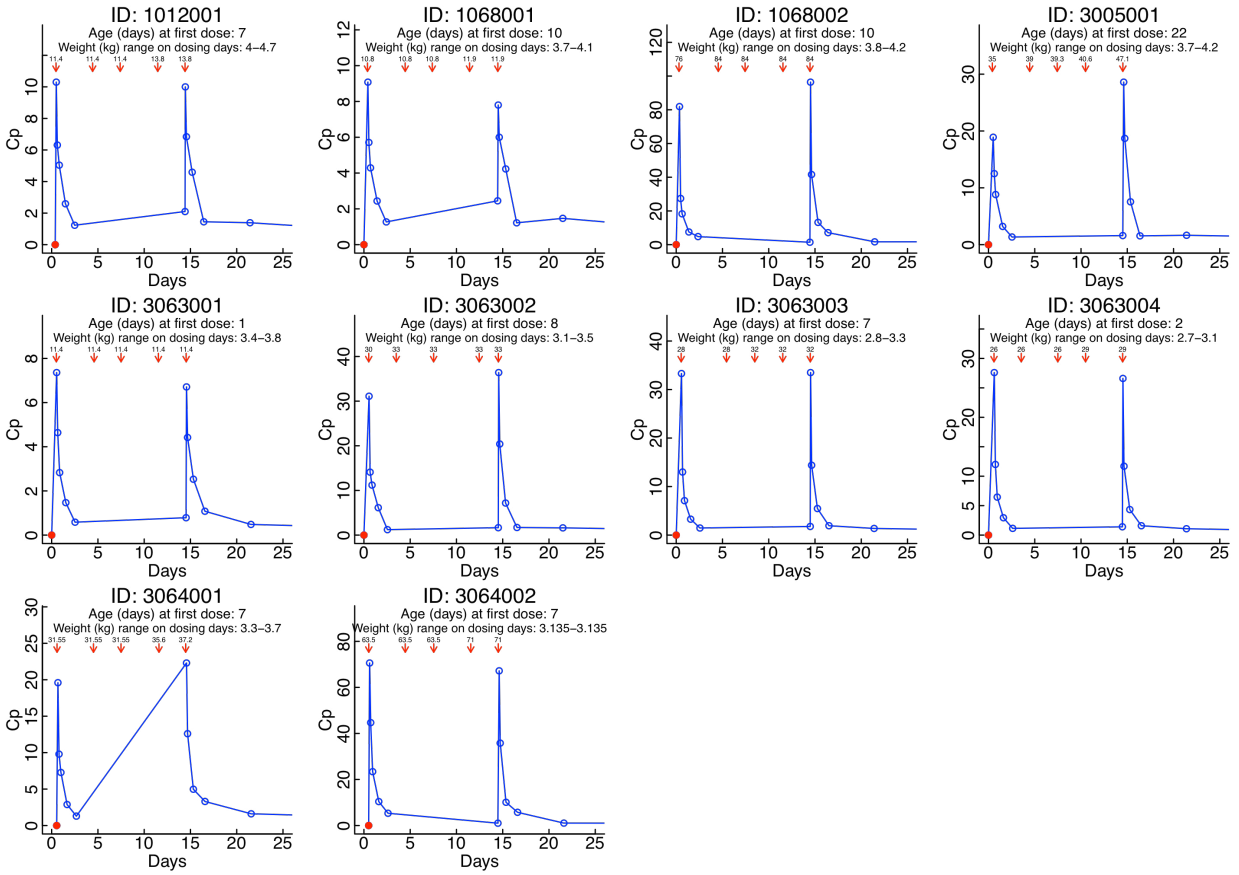

Figure 1. Serum concentration data (µg/ml) through Day 25 are displayed against time (days) for each subject. Doses are displayed as arrows (dose magnitude displayed as text). BQL values are displayed as red circles.

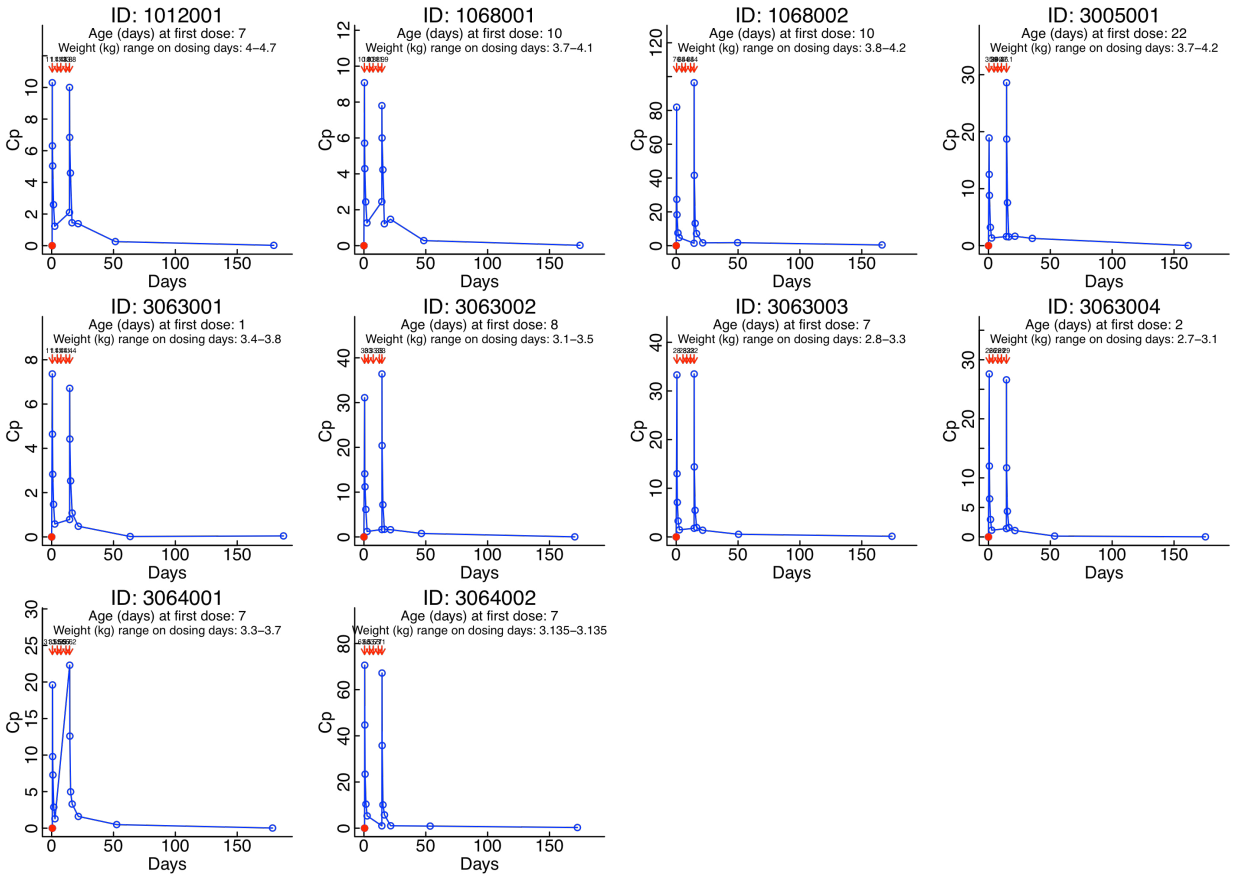

Figure 2. Serum concentration data (µg/ml) through completion of sampling are displayed against time (days) for each subject. Doses are displayed as arrows (dose magnitude displayed as text). BQL values are displayed as red circles.

Pharmacokinetic Analyses

A population pharmacokinetic analysis was performed using NONMEM (ICON Development Solutions, Hanover, MD, version 7.3.0) and PLT Tools (PLTsoft, San Francisco, CA, version 5.4.0).

Based on previous studies in adults, a three-compartment linear model with elimination from the central compartment was evaluated. Two approaches to scaling for body size were evaluated: a weight-normalized approach in which all parameters were scaled by weight and an allometric approach in which clearances are scaled by weight raised to the 0.75 power and distribution volumes are scaled by weight.

Initial analyses with both approaches demonstrated that the fit of the model to the data was markedly influenced by the Month 6 samples, six of which were reported as > LOQ. To address the impact of these samples, three sets of NONMEM runs were performed:

Set 1: All pre-dose BQL samples were excluded from the analysis (by setting NONMEM's `EVID` option to 2). Post-dose BQL samples were assigned the value LOQ / 2 and were included in the analysis.

Set 2: All pre-dose and post-dose BQL samples were excluded from the analysis.

Set 3: All pre-dose and post-dose BQL samples and samples at Month 6 were excluded from the analysis.

Within each set, four runs were performed, two with weight-normalizing scaling and two with allometric scaling. For each of weight-normalized scaling and allometric scaling, the initial run included two terms in the model for residual error, one proportional to the prediction, the other additive. In each instance, the estimate of variance of the additive term was vanishingly small, suggesting that the additive term was not needed in the model (and in a number of cases, including that term prevented NONMEM from achieving 3.0 significant digits). As a result, a second run was performed in which variance of the additive term was fixed to zero, thereby removing that term from the model.

NONMEM runs are summarized briefly in **Table 1**, **Table 2**, and **Table 3**.

Table 1. Summary of all NONMEM runs in Set 1 (post-dose BQL used in the analysis).

Run #	Timestamp	Objective Function	Significant Digits	Comments
1	160502-113133	107.597	Unreportable	Weight-normalized
2	160503-071641	140.399	3.1	Run #1 minus additive sigma
3	160502-111312	108.220	Unreportable	Allometric
4	160503-075203	138.680	3.3	Run #3 minus additive sigma

Table 2. Summary of all NONMEM runs in Set 2 (post-dose BQL not used in the analysis).

Run #	Timestamp	Objective Function	Significant Digits	Comments
5	160502-113210	150.771	Unreportable	Weight-normalized
6	160503-071652	157.466	3.1	Run #5 minus additive sigma
7	160502-111322	151.574	Unreportable	Allometric
8	160503-074922	156.560	3.1	Run #7 minus additive sigma

Table 3. Summary of all NONMEM runs in Set 3 (post-dose BQL and Month 6 samples excluded from the analysis).

Run #	Timestamp	Objective Function	Significant Digits	Comments
9	160502-150853	165.666	Unreportable	Weight-normalized
10	160502-150906	165.666	Unreportable	Run #9 minus additive sigma
11	160502-150845	166.737	3.0	Allometric
12	160503-071711	166.739	Unreportable	Run #11 minus additive sigma

Set 1 (post-dose BQL samples included in the analysis):

Each of the runs with two terms in the error model (Run #1 [**Figure 3**], Run #3) were generally unbiased through the Month 2 samples but was significantly biased at the Month 6 samples. The two runs that excluded the additive term from the error model (Run #2 [**Figure 4**], Run #4) were generally unbiased throughout the time course (including the Month 6 samples). However, removing the additive term from the error model markedly increased the objective function for both the weight-normalized and allometric models (32.802 and 30.460 units, respectively). Differences between the weight-normalized and allometric models were trivial, as assessed by various goodness-of-fit graphics.

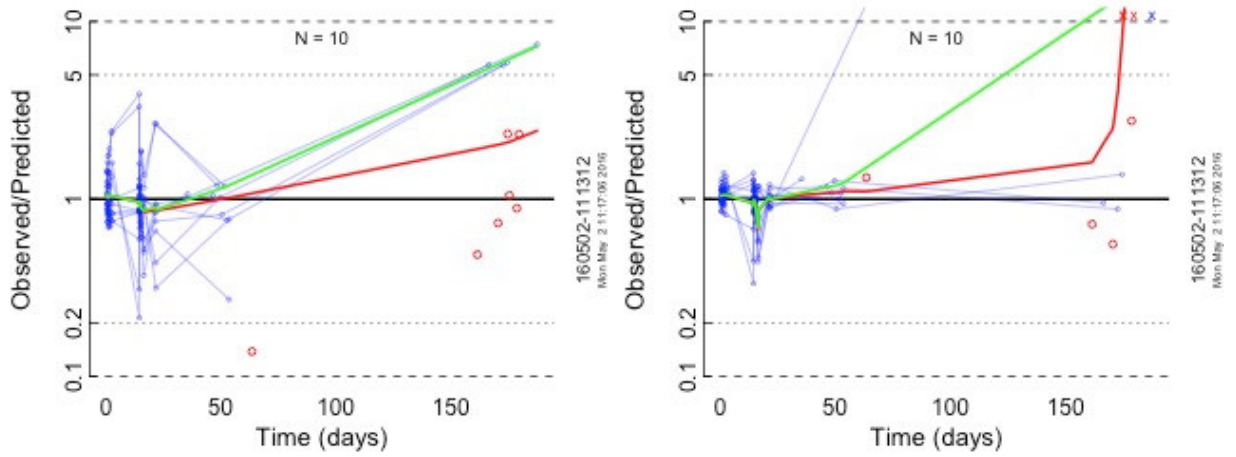

Figure 3. Run #1: Goodness-of-fit graphics. For each subject, a thin blue line displays the ratio of observed to population predicted concentrations against time. The thick lines (smoothers [Supersmoother®]) deviate from the thick black line of unity; the green line excludes BQL values whereas the red line includes those values.

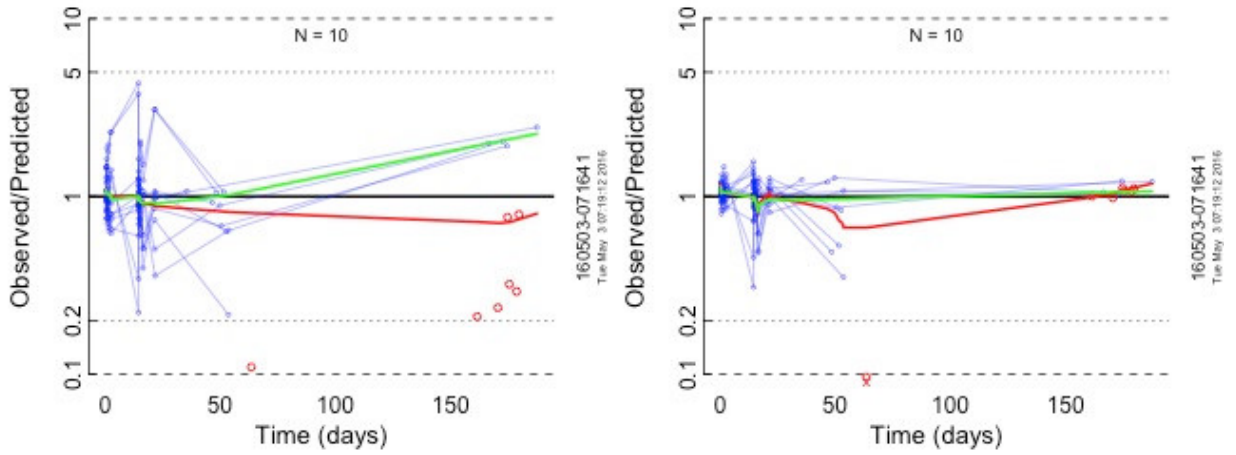

Figure 4. Run #2: Goodness-of-fit graphics. For each subject, a thin blue line displays the ratio of observed to population predicted concentrations against time. The thick lines (smoothers [Supersmoother®]) deviate from the thick black line of unity; the green line excludes BQL values whereas the red line includes those values.

Set 2 (post-dose BQL samples not included in the analysis):

Each of the four runs (Run #5 [**Figure 5**], Run #6, Run #7, Run #8) were generally unbiased through the Month 2 samples but was significantly biased at the Month 6 samples. Differences between the weight-normalized and allometric models were trivial, as assessed by various goodness-of-fit graphics (not shown) and the objective function.

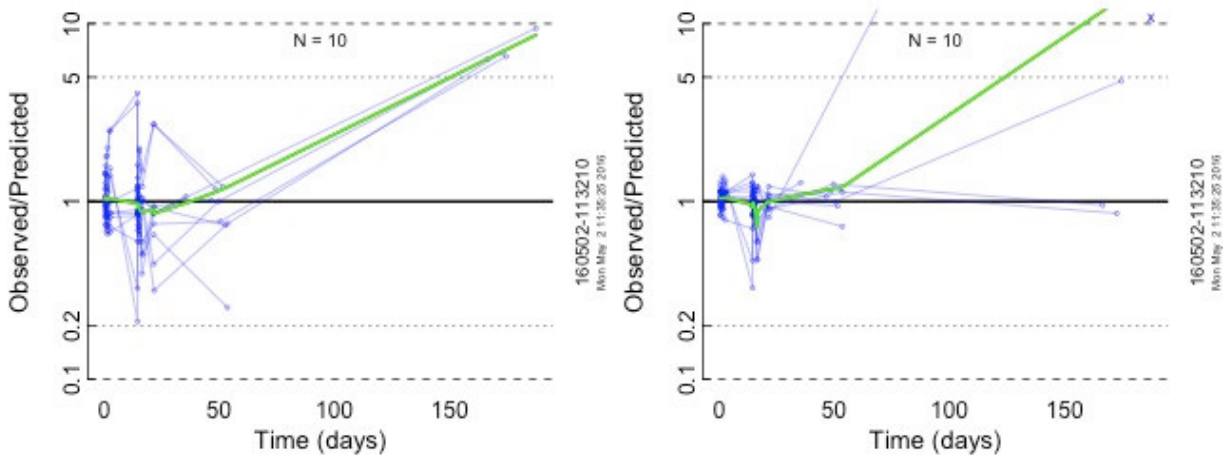

Figure 5. Run #5: Goodness-of-fit graphics. For each subject, a thin blue line displays the ratio of observed to population predicted concentrations against time. The thick lines (smoothers [Supersmoother®]) deviate from the thick black line of unity; the green line excludes BQL values whereas the red line includes those values.

Set 3 (post-dose BQL samples and Month 6 not included in the analysis):

Each of the four runs (Run #9 [**Figure 6**], Run #10, Run 11, Run #12) was generally unbiased throughout the time course (including the Month 6 samples). Differences between the weight-normalized and allometric models were trivial, as assessed by various goodness-of-fit graphics (not shown) and the objective function.

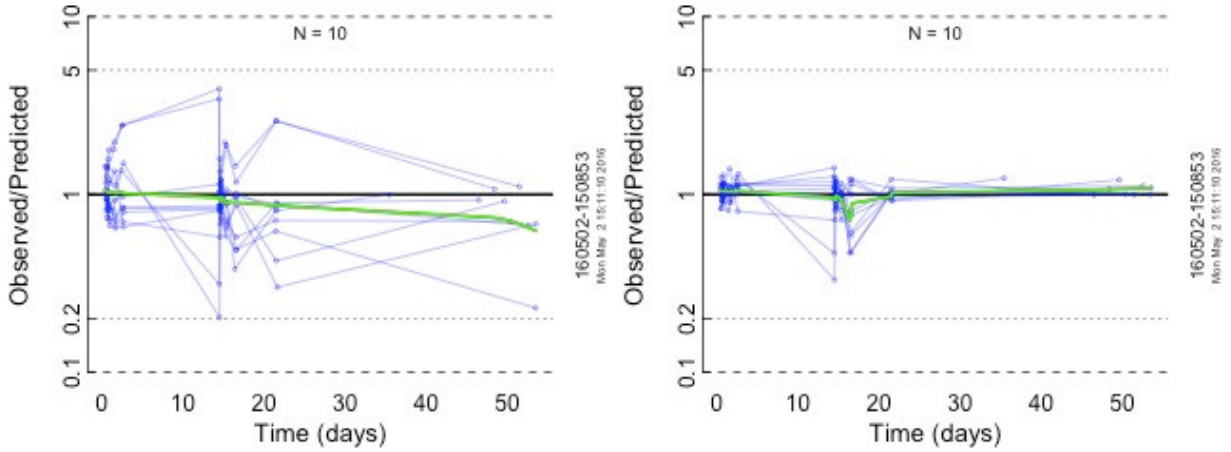

Figure 6. Run #9: Goodness-of-fit graphics. For each subject, a thin blue line displays the ratio of observed to population predicted concentrations against time. The thick lines (smoothers [Supersmoother®]) deviate from the thick black line of unity; the green line excludes BQL values whereas the red line includes those values.

Comparison of Weight-Normalization vs. Allometric Scaling

Within each set, there was a downward trend in the *eta* term for clearance for each of the weight-normalized and allometric-scaled models (graphics for Set 1 are displayed in **Figure 7**). However, these trends were not statistically significant for any of the runs,

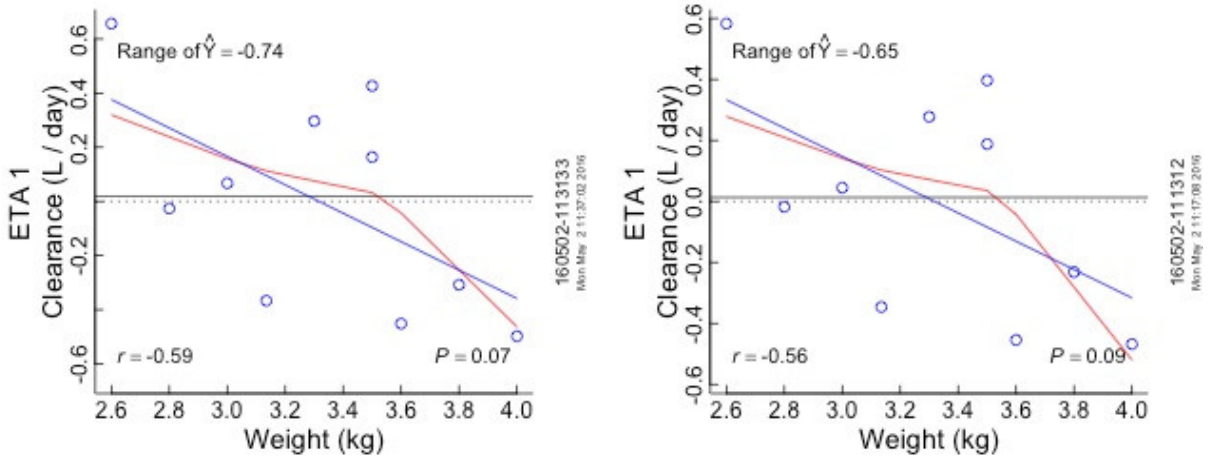

Figure 7. *Post hoc etas* for clearance (left: Run #1 [weight-normalized model]; right: Run #3 [allometric]) are displayed against weight. The red line is a smoother (Supersmoother); the blue line is a linear regression (*P*, *r*, and range of fitted y-values displayed).

Differences Between Regions

For all runs, *post hoc etas* for clearance (**Figure 8**) were smaller for subjects in the United States compared to subjects in Europe.

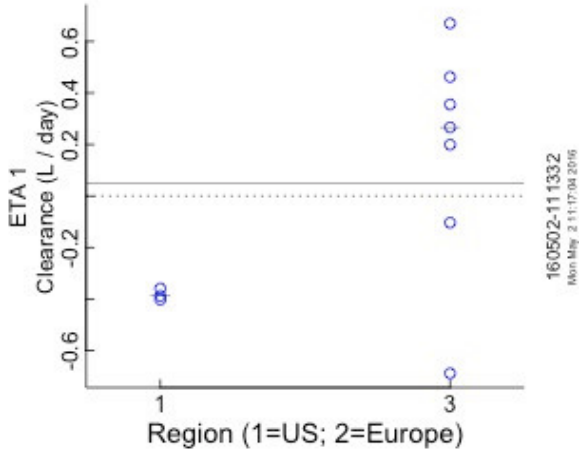

Figure 7. *Post hoc etas* for clearance (Run #1) are displayed against region. Regions differ (*P* = 0.02 by Student's t test for unpaired data).

Values for Clearance

Values for clearance were generally similar for each of the weight-normalized models (**Table 4**) and for each of the allometric-scaled models (**Table 5**), despite the large impact of the Month 6 data on quality-of-fit graphics. For each of Set 1 and Set 2, the model with one error term had a smaller clearance compared to the model with two error terms.

Table 4. Values for Apparent Clearance for Weight-Normalized Models (normalized to a weight of 86.8 kg)

Set	# of Error Terms	Clearance (L/hour)
1	2	24.287
1	1	21.399
2	2	24.322
2	1	21.428
3	2	22.876
3	2	22.878

Table 5. Values for Apparent Clearance for Allometric-Scaled Models (normalized to an allometrically-scaled weight of 86.8 kg)

Set	# of Error Terms	Clearance (L/hour)
1	2	11.465
1	1	10.243
2	2	11.290
2	1	10.162
3	2	10.662
3	2	10.663

Conclusions

Comparison to Adults: The value for clearance in all of the weight-normalized models was similar to that determined in adults (**Table 6**).

Table 6. Pharmacokinetic parameters from the optimal weight-normalized model in adults.

Parameter	Typical Value
Clearance (L /day)	21.4507 • (WT / 86.8)
Volume of the central compartment (L)	7.87249 • (WT / 86.8)
Distribution clearance (L /day)	92.4160 • (WT / 86.8)
Volume of the peripheral compartment (L)	19.7833 • (WT / 86.8)
Slow distribution clearance (L / day)	13.9319 • (WT / 86.8)
Volume of the deep peripheral compartment (L)	76.1963 • (WT / 86.8)

Differences Between Regions: A difference between regions was identified in an interim analysis and is confirmed in the present analysis. An investigation by Edimer did not reveal any issues related to study conduct (*e.g.*, handling of drug) to explain this difference.

Allometric vs. Weight-Normalized Scaling: Differences in fit (assessed visually and by the objective function) between the weight-normalized and allometric approaches were trivial. Most likely, this is the result of the narrow range of weights for subjects in the present study. Differences between the allometric and weight-normalized values are a result of the scaling term. For example, for the models with two error terms in Set 1, clearance for a 4.0-kg subject is 1.12 L/hour (24.287 • 4.0/86.8) with the weight-normalized model and 1.14 L/hour (11.465 • $(4.0/86.8)^{0.75}$) for the allometric model. Differences between the allometric and weight-normalized models would become important if EDI200 were administered to children with a broader range of weight.

Impact of Month 6 Samples: Graphics (*e.g.,* comparison of **Figure 3** and **Figure 6**) suggested a marked impact of inclusion of Month 6 data on the quality of fit of the models to the data. Although values for clearance differed between the three sets of analyses (**Table 4**, **Table 5**), the impact on clearance was relatively small. Thus, the values displayed in these tables can be considered as reasonable estimates for this population.

Appendix 16.7- Individual Subject Immunogenicity Listing

Study Title	Subject	Date Collected	Time Collected	Sample Number	Result
ECP-002	1012-001	26-Nov-13	9:15	Baseline	Negative
ECP-002		18-Dec-13	10:30	Day 16	Negative
ECP-002		22-Jan-14	11:30	Month 2	Negative
ECP-002		30-May-14	14:06	Month 6	Negative
ECP-002	1068-001	3-Mar-14	14:14	Baseline	Negative
ECP-002		21-Mar-14	12:12	Day 16	Negative
ECP-002		22-Apr-14	9:26	Month 2	Negative
ECP-002		26-Aug-14	16:00	Month 6	Negative
ECP-002	1068-002	25-Feb-15	10:35	Baseline	Negative
ECP-002		15-Mar-15	9:47	Day 16	Negative
ECP-002		17-Apr-15	14:35	Month 2	Negative
ECP-002		12-Aug-15	9:44	Month 6	Negative
ECP-002	3005-001	31-Jul-14	10:20	Baseline	Negative
ECP-002		31-Jul-14	10:20	Day 16	Negative
ECP-002		8-Sep-14	10:00	Month 2	Negative
ECP-002		12-Jan-15	10:45	Month 6	Negative
ECP-002	3063-001	17-Sep-13	8:10	Baseline	Negative
ECP-002		4-Oct-13	11:30	Day 16	Negative
ECP-002		20-Nov-13	10:30	Month 2	Negative
ECP-002		24-Mar-14	10:00	Month 6	Negative
ECP-002	3063-002	29-Oct-14	13:20	Baseline	Negative
ECP-002		18-Nov-14	13:00	Day 16	Negative
ECP-002		18-Dec-14	11:40	Month 2	Negative
ECP-002		21-Apr-15	11:05	Month 6	Negative
ECP-002	3063-003	24-Nov-14	12:40	Baseline	Negative
ECP-002		12-Dec-14	12:15	Day 16	Negative
ECP-002		15-Jan-15	9:00	Month 2	Negative
ECP-002		19-May-15	10:15	Month 6	Negative
ECP-002	3063-004	4-Jan-15	14:00	Baseline	Negative
ECP-002		21-Jan-15	12:30	Day 16	Negative
ECP-002		27-Feb-15	11:15	Month 2	Negative
ECP-002		29-Jun-15	9:30	Month 6	Negative
ECP-002	3064-001	9-May-14	13:00	Baseline	Negative
ECP-002		25-May-14	14:15	Day 16	Negative
ECP-002		30-Jun-14	13:15	Month 2	Negative
ECP-002		3-Nov-14	14:05	Month 6	Negative
ECP-002	3064-002	9-Apr-15	12:15	Baseline	Negative
ECP-002		25-Apr-15	14:30	Day 16	Negative
ECP-002		1-Jun-15	12:30	Month 2	Negative
ECP-002		28-Sep-15	14:00	Month 6	Negative

14. TABLES REFERRED TO BUT NOT INCLUDED IN THE TEXT

Table 14.1.1 Subject Disposition

	Cohort 1 N=3	Cohort 2 N=5	Cohort 3 N=2	Overall N=10
Did the subject receive all study drug per the protocol?				
Yes	3 (100%)	5 (100%)	2 (100%)	10 (100%)
Did the subject complete the study?				
Yes	3 (100%)	5 (100%)	2 (100%)	10 (100%)

Percentages are based on the total number of patients in each group (N).

Cross Reference: Listing 16.2.1

Table 14.2.1.1 Summary of Growth and Development: Bayley Scales of Infant Development II - Mental Scale

		Raw Score						Development Index					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Month 2	1	10.0		10.0	10	10	1	64.0		64.0	64	64
	Month 4	1	37.0		37.0	37	37	1	85.0		85.0	85	85
	Month 6	1	55.0		55.0	55	55	1	84.0		84.0	84	84
Cohort 2	Month 2	3	18.7	8.74	21.0	9	26	3	90.7	5.03	90.0	86	96
	Month 4	3	39.0	3.46	41.0	35	41	3	96.3	5.77	93.0	93	103
	Month 6	3	58.3	2.31	57.0	57	61	3	95.7	7.51	96.0	88	103
Overall	Month 2	4	16.5	8.35	15.5	9	26	4	84.0	13.95	88.0	64	96
	Month 4	4	38.5	3.00	39.0	35	41	4	93.5	7.37	93.0	85	103
	Month 6	4	57.5	2.52	57.0	55	61	4	92.8	8.46	92.0	84	103

n represents the number of subjects contributing to summary statistics at each visit.

Cross Reference: Listing 16.2.6.4

Table 14.2.1.1 Summary of Growth and Development: Bayley Scales of Infant Development II - Motor Scale

		Raw Score						Development Index					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Month 2	1	13.0		13.0	13	13	1	90.0		90.0	90	90
	Month 4	1	25.0		25.0	25	25	1	89.0		89.0	89	89
	Month 6	1	38.0		38.0	38	38	1	94.0		94.0	94	94
Cohort 2	Month 2	3	14.7	5.77	18.0	8	18	3	99.3	9.81	105.0	88	105
	Month 4	3	24.0	3.00	24.0	21	27	3	89.7	4.73	88.0	86	95
	Month 6	3	34.3	2.08	35.0	32	36	3	89.0	4.58	88.0	85	94
Overall	Month 2	4	14.3	4.79	15.5	8	18	4	97.0	9.27	97.5	88	105
	Month 4	4	24.3	2.50	24.5	21	27	4	89.5	3.87	88.5	86	95
	Month 6	4	35.3	2.50	35.5	32	38	4	90.3	4.50	91.0	85	94

n represents the number of subjects contributing to summary statistics at each visit.

Cross Reference: Listing 16.2.6.4

Table 14.2.1.2 Summary of Growth and Development: Bayley Scales of Infant Development III - Motor Composite Score

		Sum of Scaled Scores						Composite Score					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Month 2	1	18.0		18.0	18	18	1	94.0		94.0	94	94
	Month 4	1	22.0		22.0	22	22	1	107.0		107.0	107	107
	Month 6	1	27.0		27.0	27	27	1	121.0		121.0	121	121
Cohort 2	Month 2	1	17.0		17.0	17	17	1	91.0		91.0	91	91
	Month 4	1	19.0		19.0	19	19	1	97.0		97.0	97	97
	Month 6	1	20.0		20.0	20	20	1	100.0		100.0	100	100
Cohort 3	Month 2	1	22.0		22.0	22	22	1	107.0		107.0	107	107
	Month 4	1	27.0		27.0	27	27	1	121.0		121.0	121	121
	Month 6	1	15.0		15.0	15	15	1	85.0		85.0	85	85
Overall	Month 2	3	19.0	2.65	18.0	17	22	3	97.3	8.50	94.0	91	107
	Month 4	3	22.7	4.04	22.0	19	27	3	108.3	12.06	107.0	97	121
	Month 6	3	20.7	6.03	20.0	15	27	3	102.0	18.08	100.0	85	121

n represents the number of subjects contributing to summary statistics at each visit.

Cross Reference: Listing 16.2.6.4

Table 14.2.1.2 Summary of Growth and Development: Bayley Scales of Infant Development III

Cognitive Comprehensive Score

		Sum of Scaled Scores						Composite Score					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Month 2	1	7.0		7.0	7	7	1	85.0		85.0	85	85
	Month 4	1	12.0		12.0	12	12	1	110.0		110.0	110	110
	Month 6	1	11.0		11.0	11	11	1	105.0		105.0	105	105
Cohort 2	Month 2	1	12.0		12.0	12	12	1	110.0		110.0	110	110
	Month 4	1	11.0		11.0	11	11	1	105.0		105.0	105	105
	Month 6	1	10.0		10.0	10	10	1	100.0		100.0	100	100
Cohort 3	Month 2	1	11.0		11.0	11	11	1	105.0		105.0	105	105
	Month 4	1	13.0		13.0	13	13	1	115.0		115.0	115	115
	Month 6	1	10.0		10.0	10	10	1	100.0		100.0	100	100
Overall	Month 2	3	10.0	2.65	11.0	7	12	3	100.0	13.23	105.0	85	110
	Month 4	3	12.0	1.00	12.0	11	13	3	110.0	5.00	110.0	105	115
	Month 6	3	10.3	0.58	10.0	10	11	3	101.7	2.89	100.0	100	105

n represents the number of subjects contributing to summary statistics at each visit.

Cross Reference: Listing 16.2.6.4

Table 14.3.1.1 Overall Summary of Treatment Emergent Adverse Events

	Cohort 1 (N=3)		Cohort 2 (N=5)		Cohort 3 (N=2)		Overall (N=10)		Siblings (N=4)	
	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n
Patients with at Least One TEAE	3 (100%)	49	5 (100%)	70	2 (100%)	47	10 (100%)	166	1 (25.0%)	3
Relationship to Study Treatment										
Definitely	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0
Probably	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Possibly	1 (33.3%)	13	2 (40.0%)	27	1 (50.0%)	1	4 (40.0%)	41	0 (0.0%)	0
Unlikely	2 (66.7%)	30	2 (40.0%)	19	1 (50.0%)	27	5 (50.0%)	76	0 (0.0%)	0
Not Related	0 (0.0%)	6	0 (0.0%)	23	0 (0.0%)	19	0 (0.0%)	48	0 (0.0%)	0
CTCAE Grade										
Mild	1 (33.3%)	46	1 (20.0%)	63	0 (0.0%)	45	2 (20.0%)	154	0 (0.0%)	1
Moderate	1 (33.3%)	1	2 (40.0%)	2	1 (50.0%)	1	4 (40.0%)	4	1 (25.0%)	2
Severe	1 (33.3%)	2	2 (40.0%)	3	1 (50.0%)	1	4 (40.0%)	6	0 (0.0%)	0
Life Threatening	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0
Death Related to AE	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0
IA Grade										
Mild	2 (66.7%)	48	1 (20.0%)	65	0 (0.0%)	45	3 (30.0%)	158	0 (0.0%)	1
Moderate	0 (0.0%)	0	3 (60.0%)	3	1 (50.0%)	1	4 (40.0%)	4	1 (25.0%)	2
Severe	1 (33.3%)	1	1 (20.0%)	2	1 (50.0%)	1	3 (30.0%)	4	0 (0.0%)	0
Patients with at Least One TESAE	1 (33.3%)	1	3 (60.0%)	4	1 (50.0%)	1	5 (50.0%)	6	0 (0.0%)	0

TEAE=Treatment Emergent Adverse Event; TESAE=Treatment Emergent Serious Adverse Event; IA=Per Investigator Assessment.
[1] At each level of summation (relationship, intensity), patients reporting more than one AE are counted only once using the strongest relationship to study medication and maximum intensity.
[2] Number of events includes all occurrences of events.

Cross Reference: Listing 16.2.7

Table 14.3.1.2 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Greatest Intensity (CTCAE Grade)

System Organ Class Preferred Term Intensity	Cohort 1 N=3 Number of Subjects (%)	Cohort 1 Number of Events	Cohort 2 N=5 Number of Subjects (%)	Cohort 2 Number of Events	Cohort 3 N=2 Number of Subjects (%)	Cohort 3 Number of Events	Overall N=10 Number of Subjects (%)	Overall Number of Events	Siblings N=4 Number of Subjects (%)	Siblings Number of Events
All Body Systems	3 (100%)	49	5 (100%)	70	2 (100%)	47	10 (100%)	166	1 (25.0%)	3
Mild	1 (33.3%)	46	1 (20.0%)	63	0 (0.0%)	45	2 (20.0%)	154	0 (0.0%)	1
Moderate	1 (33.3%)	1	2 (40.0%)	2	1 (50.0%)	1	4 (40.0%)	4	1 (25.0%)	2
Severe	1 (33.3%)	2	2 (40.0%)	3	1 (50.0%)	1	4 (40.0%)	6	0 (0.0%)	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2 (66.7%)	6	4 (80.0%)	7	1 (50.0%)	3	7 (70.0%)	16	1 (25.0%)	1
Mild	2 (66.7%)	6	4 (80.0%)	7	1 (50.0%)	3	7 (70.0%)	16	1 (25.0%)	1
ANAEMIA	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
EOSINOPHILIA	1 (33.3%)	1	3 (60.0%)	3	0 (0.0%)	0	4 (40.0%)	4	0 (0.0%)	0
Mild	1 (33.3%)	1	3 (60.0%)	3	0 (0.0%)	0	4 (40.0%)	4	0 (0.0%)	0
HYPOCHROMASIA	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	2	1 (10.0%)	2	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	2	1 (10.0%)	2	0 (0.0%)	0
LYMPHADENOPATHY	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (25.0%)	1
Mild	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (25.0%)	1
LYMPHOCYTOSIS	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
MACROCYTOSIS	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
MONOCYTOSIS	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
POIKILOCYTOSIS	1 (33.3%)	2	0 (0.0%)	0	1 (50.0%)	1	2 (20.0%)	3	0 (0.0%)	0
Mild	1 (33.3%)	2	0 (0.0%)	0	1 (50.0%)	1	2 (20.0%)	3	0 (0.0%)	0
RED BLOOD CELL ABNORMALITY	1 (33.3%)	2	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	2	0 (0.0%)	0
Mild	1 (33.3%)	2	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	2	0 (0.0%)	0
THROMBOCYTOSIS	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0

Note: Adverse events summarized include both serious and nonserious adverse events.
Treatment Emergent AEs are AEs that occurred after administration of study drug.
Percentages are based on the total number of subjects in each treatment group (N).
Any subject with multiple events in one System Organ Class (SOC) was counted only once for that SOC, using the event with the greatest intensity.
Any subject with multiple events in one Preferred Term (PT) was counted only once for that PT, using the event with the greatest intensity.

Cross Reference: Listing 16.2.7

Table 14.3.1.2 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Greatest Intensity (CTCAE Grade)

System Organ Class Preferred Term Intensity	Cohort 1 N=3 Number of Subjects (%)	Cohort 1 N=3 Number of Events	Cohort 2 N=5 Number of Subjects (%)	Cohort 2 N=5 Number of Events	Cohort 3 N=2 Number of Subjects (%)	Cohort 3 N=2 Number of Events	Overall N=10 Number of Subjects (%)	Overall N=10 Number of Events	Siblings N=4 Number of Subjects (%)	Siblings N=4 Number of Events
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
NAEVUS FLAMMEUS	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
GASTROINTESTINAL DISORDERS	0 (0.0%)	0	1 (20.0%)	1	2 (100%)	2	3 (30.0%)	3	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	1	2 (100%)	2	3 (30.0%)	3	0 (0.0%)	0
SALIVARY HYPERSECRETION	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
UMBILICAL HERNIA	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
VOMITING	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0 (0.0%)	0	1 (20.0%)	1	1 (50.0%)	1	2 (20.0%)	2	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Moderate	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
INJECTION SITE OEDEMA	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
MEDICAL DEVICE COMPLICATION	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Moderate	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
INFECTIONS AND INFESTATIONS	2 (66.7%)	2	4 (80.0%)	7	1 (50.0%)	1	7 (70.0%)	10	1 (25.0%)	2
Mild	1 (33.3%)	1	0 (0.0%)	2	0 (0.0%)	0	1 (10.0%)	3	0 (0.0%)	0
Moderate	0 (0.0%)	0	2 (40.0%)	2	0 (0.0%)	0	2 (20.0%)	2	1 (25.0%)	2

Note: Adverse events summarized include both serious and nonserious adverse events.
Treatment Emergent AEs are AEs that occurred after administration of study drug.
Percentages are based on the total number of subjects in each treatment group (N).
Any subject with multiple events in one System Organ Class (SOC) was counted only once for that SOC, using the event with the greatest intensity.
Any subject with multiple events in one Preferred Term (PT) was counted only once for that PT, using the event with the greatest intensity.

Cross Reference: Listing 16.2.7

Table 14.3.1.2 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Greatest Intensity (CTCAE Grade)

System Organ Class Preferred Term Intensity	Cohort 1 N=3 Number of Subjects (%)	Cohort 1 Number of Events	Cohort 2 N=5 Number of Subjects (%)	Cohort 2 Number of Events	Cohort 3 N=2 Number of Subjects (%)	Cohort 3 Number of Events	Overall N=10 Number of Subjects (%)	Overall Number of Events	Siblings N=4 Number of Subjects (%)	Siblings Number of Events
Severe	1 (33.3%)	1	2 (40.0%)	3	1 (50.0%)	1	4 (40.0%)	5	0 (0.0%)	0
BRONCHIOLITIS	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Severe	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
BRONCHOPNEUMONIA	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Severe	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
LOWER RESPIRATORY TRACT INFECTION	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Severe	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
OTITIS MEDIA	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Moderate	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
PHARYNGITIS	0 (0.0%)	0	1 (20.0%)	2	0 (0.0%)	0	1 (10.0%)	2	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	2	0 (0.0%)	0	1 (10.0%)	2	0 (0.0%)	0
PYELONEPHRITIS	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Moderate	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
RESPIRATORY SYNCYTIAL VIRUS INFECTION	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Severe	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
UPPER RESPIRATORY TRACT INFECTION	1 (33.3%)	1	1 (20.0%)	1	0 (0.0%)	0	2 (20.0%)	2	1 (25.0%)	1
Mild	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Moderate	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (25.0%)	1
Severe	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
VIRAL INFECTION	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (25.0%)	1
Moderate	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (25.0%)	1
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
PROCEDURAL SITE REACTION	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0

Note: Adverse events summarized include both serious and nonserious adverse events.
Treatment Emergent AEs are AEs that occurred after administration of study drug.
Percentages are based on the total number of subjects in each treatment group (N).
Any subject with multiple events in one System Organ Class (SOC) was counted only once for that SOC, using the event with the greatest intensity.
Any subject with multiple events in one Preferred Term (PT) was counted only once for that PT, using the event with the greatest intensity.

Cross Reference: Listing 16.2.7

Table 14.3.1.2 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Greatest Intensity (CTCAE Grade)

System Organ Class Preferred Term Intensity	Cohort 1 N=3 Number of Subjects (%)	Cohort 1 Number of Events	Cohort 2 N=5 Number of Subjects (%)	Cohort 2 Number of Events	Cohort 3 N=2 Number of Subjects (%)	Cohort 3 Number of Events	Overall N=10 Number of Subjects (%)	Overall Number of Events	Siblings N=4 Number of Subjects (%)	Siblings Number of Events
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
INVESTIGATIONS	3 (100%)	34	5 (100%)	45	2 (100%)	34	10 (100%)	113	0 (0.0%)	0
Mild	2 (66.7%)	33	5 (100%)	43	2 (100%)	34	9 (90.0%)	110	0 (0.0%)	0
Moderate	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
ALANINE AMINOTRANSFERASE INCREASED	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
ALBUMIN URINE PRESENT	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
ASPARTATE AMINOTRANSFERASE INCREASED	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
BASOPHIL COUNT DECREASED	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
BASOPHIL COUNT INCREASED	0 (0.0%)	0	4 (80.0%)	6	1 (50.0%)	1	5 (50.0%)	7	0 (0.0%)	0
Mild	0 (0.0%)	0	4 (80.0%)	6	1 (50.0%)	1	5 (50.0%)	7	0 (0.0%)	0
BLOOD ALBUMIN DECREASED	0 (0.0%)	0	1 (20.0%)	2	0 (0.0%)	0	1 (10.0%)	2	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	2	0 (0.0%)	0	1 (10.0%)	2	0 (0.0%)	0
BLOOD ALKALINE PHOSPHATASE INCREASED	0 (0.0%)	0	2 (40.0%)	2	1 (50.0%)	1	3 (30.0%)	3	0 (0.0%)	0
Mild	0 (0.0%)	0	2 (40.0%)	2	1 (50.0%)	1	3 (30.0%)	3	0 (0.0%)	0
BLOOD BICARBONATE INCREASED	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
BLOOD BILIRUBIN INCREASED	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
BLOOD CHLORIDE INCREASED	0 (0.0%)	0	3 (60.0%)	3	0 (0.0%)	0	3 (30.0%)	3	0 (0.0%)	0
Mild	0 (0.0%)	0	3 (60.0%)	3	0 (0.0%)	0	3 (30.0%)	3	0 (0.0%)	0
BLOOD CREATININE DECREASED	2 (66.7%)	3	4 (80.0%)	4	0 (0.0%)	0	6 (60.0%)	7	0 (0.0%)	0
Mild	2 (66.7%)	3	4 (80.0%)	4	0 (0.0%)	0	6 (60.0%)	7	0 (0.0%)	0

Note: Adverse events summarized include both serious and nonserious adverse events.
Treatment Emergent AEs are AEs that occurred after administration of study drug.
Percentages are based on the total number of subjects in each treatment group (N).
Any subject with multiple events in one System Organ Class (SOC) was counted only once for that SOC, using the event with the greatest intensity.
Any subject with multiple events in one Preferred Term (PT) was counted only once for that PT, using the event with the greatest intensity.

Cross Reference: Listing 16.2.7

Table 14.3.1.2 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Greatest Intensity (CTCAE Grade)

System Organ Class Preferred Term Intensity	Cohort 1 N=3 Number of Subjects (%)	Cohort 1 Number of Events	Cohort 2 N=5 Number of Subjects (%)	Cohort 2 Number of Events	Cohort 3 N=2 Number of Subjects (%)	Cohort 3 Number of Events	Overall N=10 Number of Subjects (%)	Overall Number of Events	Siblings N=4 Number of Subjects (%)	Siblings Number of Events
BLOOD CREATININE INCREASED	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
BLOOD GLUCOSE INCREASED	1 (33.3%)	1	2 (40.0%)	2	0 (0.0%)	0	3 (30.0%)	3	0 (0.0%)	0
Mild	1 (33.3%)	1	2 (40.0%)	2	0 (0.0%)	0	3 (30.0%)	3	0 (0.0%)	0
BLOOD POTASSIUM INCREASED	1 (33.3%)	1	0 (0.0%)	0	2 (100%)	2	3 (30.0%)	3	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	2 (100%)	2	3 (30.0%)	3	0 (0.0%)	0
BLOOD SODIUM DECREASED	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
BLOOD UREA DECREASED	2 (66.7%)	2	0 (0.0%)	0	1 (50.0%)	1	3 (30.0%)	3	0 (0.0%)	0
Mild	2 (66.7%)	2	0 (0.0%)	0	1 (50.0%)	1	3 (30.0%)	3	0 (0.0%)	0
BLOOD UREA INCREASED	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
BLOOD URINE PRESENT	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
EOSINOPHIL COUNT DECREASED	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
EOSINOPHIL COUNT INCREASED	1 (33.3%)	1	0 (0.0%)	0	1 (50.0%)	2	2 (20.0%)	3	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	1 (50.0%)	2	2 (20.0%)	3	0 (0.0%)	0
HAEMATOCRIT DECREASED	1 (33.3%)	2	1 (20.0%)	1	1 (50.0%)	1	3 (30.0%)	4	0 (0.0%)	0
Mild	1 (33.3%)	2	1 (20.0%)	1	1 (50.0%)	1	3 (30.0%)	4	0 (0.0%)	0
HAEMATOCRIT INCREASED	1 (33.3%)	1	1 (20.0%)	1	1 (50.0%)	1	3 (30.0%)	3	0 (0.0%)	0
Mild	1 (33.3%)	1	1 (20.0%)	1	1 (50.0%)	1	3 (30.0%)	3	0 (0.0%)	0
HAEMOGLOBIN DECREASED	1 (33.3%)	1	1 (20.0%)	1	1 (50.0%)	1	3 (30.0%)	3	0 (0.0%)	0
Mild	1 (33.3%)	1	1 (20.0%)	1	1 (50.0%)	1	3 (30.0%)	3	0 (0.0%)	0
HAEMOGLOBIN INCREASED	1 (33.3%)	1	1 (20.0%)	1	1 (50.0%)	2	3 (30.0%)	4	0 (0.0%)	0
Mild	1 (33.3%)	1	1 (20.0%)	1	1 (50.0%)	2	3 (30.0%)	4	0 (0.0%)	0
LYMPHOCYTE COUNT INCREASED	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0

Note: Adverse events summarized include both serious and nonserious adverse events.
Treatment Emergent AEs are AEs that occurred after administration of study drug.
Percentages are based on the total number of subjects in each treatment group (N).
Any subject with multiple events in one System Organ Class (SOC) was counted only once for that SOC, using the event with the greatest intensity.
Any subject with multiple events in one Preferred Term (PT) was counted only once for that PT, using the event with the greatest intensity.

Cross Reference: Listing 16.2.7

Table 14.3.1.2 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Greatest Intensity (CTCAE Grade)

System Organ Class Preferred Term Intensity	Cohort 1 N=3 Number of Subjects (%)	Cohort 1 Number of Events	Cohort 2 N=5 Number of Subjects (%)	Cohort 2 Number of Events	Cohort 3 N=2 Number of Subjects (%)	Cohort 3 Number of Events	Overall N=10 Number of Subjects (%)	Overall Number of Events	Siblings N=4 Number of Subjects (%)	Siblings Number of Events
Mild	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
LYMPHOCYTE MORPHOLOGY ABNORMAL	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
MEAN CELL HAEMOGLOBIN DECREASED	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
MEAN CELL HAEMOGLOBIN INCREASED	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
MONOCYTE COUNT DECREASED	1 (33.3%)	1	1 (20.0%)	1	1 (50.0%)	1	3 (30.0%)	3	0 (0.0%)	0
Mild	1 (33.3%)	1	1 (20.0%)	1	1 (50.0%)	1	3 (30.0%)	3	0 (0.0%)	0
MONOCYTE COUNT INCREASED	1 (33.3%)	1	4 (80.0%)	5	0 (0.0%)	0	5 (50.0%)	6	0 (0.0%)	0
Mild	1 (33.3%)	1	4 (80.0%)	5	0 (0.0%)	0	5 (50.0%)	6	0 (0.0%)	0
NEUTROPHIL COUNT DECREASED	2 (66.7%)	2	1 (20.0%)	1	0 (0.0%)	0	3 (30.0%)	3	0 (0.0%)	0
Mild	1 (33.3%)	1	1 (20.0%)	1	0 (0.0%)	0	2 (20.0%)	2	0 (0.0%)	0
Moderate	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
NEUTROPHIL COUNT INCREASED	0 (0.0%)	0	3 (60.0%)	4	0 (0.0%)	0	3 (30.0%)	4	0 (0.0%)	0
Mild	0 (0.0%)	0	3 (60.0%)	4	0 (0.0%)	0	3 (30.0%)	4	0 (0.0%)	0
OXYGEN SATURATION DECREASED	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
PCO2 INCREASED	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
PH URINE INCREASED	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
PLATELET COUNT INCREASED	1 (33.3%)	2	2 (40.0%)	2	1 (50.0%)	1	4 (40.0%)	5	0 (0.0%)	0
Mild	1 (33.3%)	2	2 (40.0%)	2	1 (50.0%)	1	4 (40.0%)	5	0 (0.0%)	0
PLATELET MORPHOLOGY ABNORMAL	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
PO2 DECREASED	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0

Note: Adverse events summarized include both serious and nonserious adverse events.
Treatment Emergent AEs are AEs that occurred after administration of study drug.
Percentages are based on the total number of subjects in each treatment group (N).
Any subject with multiple events in one System Organ Class (SOC) was counted only once for that SOC, using the event with the greatest intensity.
Any subject with multiple events in one Preferred Term (PT) was counted only once for that PT, using the event with the greatest intensity.

Cross Reference: Listing 16.2.7

Table 14.3.1.2 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Greatest Intensity (CTCAE Grade)

System Organ Class Preferred Term Intensity	Cohort 1 N=3 Number of Subjects (%)	Cohort 1 Number of Events	Cohort 2 N=5 Number of Subjects (%)	Cohort 2 Number of Events	Cohort 3 N=2 Number of Subjects (%)	Cohort 3 Number of Events	Overall N=10 Number of Subjects (%)	Overall Number of Events	Siblings N=4 Number of Subjects (%)	Siblings Number of Events
Mild	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
PROTEIN TOTAL DECREASED	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
PROTEIN URINE	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
RED BLOOD CELL COUNT INCREASED	2 (66.7%)	2	1 (20.0%)	1	0 (0.0%)	0	3 (30.0%)	3	0 (0.0%)	0
Mild	2 (66.7%)	2	1 (20.0%)	1	0 (0.0%)	0	3 (30.0%)	3	0 (0.0%)	0
RED BLOOD CELL ELLIPTOCYTES PRESENT	1 (33.3%)	1	0 (0.0%)	0	1 (50.0%)	1	2 (20.0%)	2	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	1 (50.0%)	1	2 (20.0%)	2	0 (0.0%)	0
RED BLOOD CELL MACROCYTES PRESENT	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	2	1 (10.0%)	2	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	2	1 (10.0%)	2	0 (0.0%)	0
RED BLOOD CELL MICROCYTES PRESENT	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
RED BLOOD CELL SCHISTOCYTES PRESENT	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
RED BLOOD CELL SPHEROCYTES PRESENT	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
SPECIFIC GRAVITY URINE DECREASED	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
SPECIFIC GRAVITY URINE INCREASED	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
URINE ANALYSIS ABNORMAL	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	3	1 (10.0%)	3	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	3	1 (10.0%)	3	0 (0.0%)	0
URINE LEUKOCYTE ESTERASE POSITIVE	1 (33.3%)	1	0 (0.0%)	0	1 (50.0%)	1	2 (20.0%)	2	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	1 (50.0%)	1	2 (20.0%)	2	0 (0.0%)	0
WHITE BLOOD CELL COUNT INCREASED	0 (0.0%)	0	3 (60.0%)	5	0 (0.0%)	0	3 (30.0%)	5	0 (0.0%)	0
Mild	0 (0.0%)	0	2 (40.0%)	3	0 (0.0%)	0	2 (20.0%)	3	0 (0.0%)	0

Note: Adverse events summarized include both serious and nonserious adverse events.
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Any subject with multiple events in one Preferred Term (PT) was counted only once for that PT, using the event with the greatest intensity.

Cross Reference: Listing 16.2.7

Table 14.3.1.2 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Greatest Intensity (CTCAE Grade)

System Organ Class Preferred Term Intensity	Cohort 1 N=3 Number of Subjects (%)	Cohort 1 Number of Events	Cohort 2 N=5 Number of Subjects (%)	Cohort 2 Number of Events	Cohort 3 N=2 Number of Subjects (%)	Cohort 3 Number of Events	Overall N=10 Number of Subjects (%)	Overall Number of Events	Siblings N=4 Number of Subjects (%)	Siblings Number of Events
METABOLISM AND NUTRITION DISORDERS	1 (33.3%)	3	3 (60.0%)	4	0 (0.0%)	0	4 (40.0%)	7	0 (0.0%)	0
Mild	0 (0.0%)	2	3 (60.0%)	4	0 (0.0%)	0	3 (30.0%)	6	0 (0.0%)	0
Severe	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
HYPERCALCAEMIA	0 (0.0%)	0	1 (20.0%)	2	0 (0.0%)	0	1 (10.0%)	2	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	2	0 (0.0%)	0	1 (10.0%)	2	0 (0.0%)	0
HYPERCHLORAEMIA	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
HYPOALBUMINAEMIA	1 (33.3%)	2	1 (20.0%)	1	0 (0.0%)	0	2 (20.0%)	3	0 (0.0%)	0
Mild	1 (33.3%)	2	1 (20.0%)	1	0 (0.0%)	0	2 (20.0%)	3	0 (0.0%)	0
HYPONATRAEMIA	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Severe	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	2	1 (10.0%)	2	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	2	1 (10.0%)	2	0 (0.0%)	0
NEONATAL DISORDER	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	2	1 (10.0%)	2	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	2	1 (10.0%)	2	0 (0.0%)	0
PSYCHIATRIC DISORDERS	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
IRRITABILITY	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
RENAL AND URINARY DISORDERS	1 (33.3%)	2	0 (0.0%)	0	1 (50.0%)	1	2 (20.0%)	3	0 (0.0%)	0
Mild	1 (33.3%)	2	0 (0.0%)	0	1 (50.0%)	1	2 (20.0%)	3	0 (0.0%)	0
URINE ABNORMALITY	1 (33.3%)	2	0 (0.0%)	0	1 (50.0%)	1	2 (20.0%)	3	0 (0.0%)	0
Mild	1 (33.3%)	2	0 (0.0%)	0	1 (50.0%)	1	2 (20.0%)	3	0 (0.0%)	0

Note: Adverse events summarized include both serious and nonserious adverse events.
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Cross Reference: Listing 16.2.7

Table 14.3.1.2 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Greatest Intensity (CTCAE Grade)

System Organ Class Preferred Term Intensity	Cohort 1 N=3 Number of Subjects (%)	Cohort 1 Number of Events	Cohort 2 N=5 Number of Subjects (%)	Cohort 2 Number of Events	Cohort 3 N=2 Number of Subjects (%)	Cohort 3 Number of Events	Overall N=10 Number of Subjects (%)	Overall Number of Events	Siblings N=4 Number of Subjects (%)	Siblings Number of Events
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
NASAL CONGESTION	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (33.3%)	1	1 (20.0%)	4	1 (50.0%)	1	3 (30.0%)	6	0 (0.0%)	0
Mild	1 (33.3%)	1	1 (20.0%)	4	1 (50.0%)	1	3 (30.0%)	6	0 (0.0%)	0
DERMATITIS	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
DRY SKIN	0 (0.0%)	0	1 (20.0%)	2	0 (0.0%)	0	1 (10.0%)	2	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	2	0 (0.0%)	0	1 (10.0%)	2	0 (0.0%)	0
HAIR DISORDER	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
HAIR GROWTH ABNORMAL	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
RASH	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0

Note: Adverse events summarized include both serious and nonserious adverse events.
Treatment Emergent AEs are AEs that occurred after administration of study drug.
Percentages are based on the total number of subjects in each treatment group (N).
Any subject with multiple events in one System Organ Class (SOC) was counted only once for that SOC, using the event with the greatest intensity.
Any subject with multiple events in one Preferred Term (PT) was counted only once for that PT, using the event with the greatest intensity.

Cross Reference: Listing 16.2.7

Table 14.3.1.3 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Greatest Intensity (Per Investigator Assessment)

System Organ Class Preferred Term Intensity	Cohort 1 N=3 Number of Subjects (%)	Cohort 1 Number of Events	Cohort 2 N=5 Number of Subjects (%)	Cohort 2 Number of Events	Cohort 3 N=2 Number of Subjects (%)	Cohort 3 Number of Events	Overall N=10 Number of Subjects (%)	Overall Number of Events	Siblings N=4 Number of Subjects (%)	Siblings Number of Events
All Body Systems	3 (100%)	49	5 (100%)	70	2 (100%)	47	10 (100%)	166	1 (25.0%)	3
Mild	2 (66.7%)	48	1 (20.0%)	65	0 (0.0%)	45	3 (30.0%)	158	0 (0.0%)	1
Moderate	0 (0.0%)	0	3 (60.0%)	3	1 (50.0%)	1	4 (40.0%)	4	1 (25.0%)	2
Severe	1 (33.3%)	1	1 (20.0%)	2	1 (50.0%)	1	3 (30.0%)	4	0 (0.0%)	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2 (66.7%)	6	4 (80.0%)	7	1 (50.0%)	3	7 (70.0%)	16	1 (25.0%)	1
Mild	2 (66.7%)	6	4 (80.0%)	7	1 (50.0%)	3	7 (70.0%)	16	1 (25.0%)	1
ANAEMIA	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
EOSINOPHILIA	1 (33.3%)	1	3 (60.0%)	3	0 (0.0%)	0	4 (40.0%)	4	0 (0.0%)	0
Mild	1 (33.3%)	1	3 (60.0%)	3	0 (0.0%)	0	4 (40.0%)	4	0 (0.0%)	0
HYPOCHROMASIA	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	2	1 (10.0%)	2	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	2	1 (10.0%)	2	0 (0.0%)	0
LYMPHADENOPATHY	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (25.0%)	1
Mild	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (25.0%)	1
LYMPHOCYTOSIS	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
MACROCYTOSIS	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
MONOCYTOSIS	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
POIKILOCYTOSIS	1 (33.3%)	2	0 (0.0%)	0	1 (50.0%)	1	2 (20.0%)	3	0 (0.0%)	0
Mild	1 (33.3%)	2	0 (0.0%)	0	1 (50.0%)	1	2 (20.0%)	3	0 (0.0%)	0
RED BLOOD CELL ABNORMALITY	1 (33.3%)	2	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	2	0 (0.0%)	0
Mild	1 (33.3%)	2	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	2	0 (0.0%)	0
THROMBOCYTOSIS	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0

Note: Adverse events summarized include both serious and nonserious adverse events.
Treatment Emergent AEs are AEs that occurred after administration of study drug.
Percentages are based on the total number of subjects in each treatment group (N).
Any subject with multiple events in one System Organ Class (SOC) was counted only once for that SOC, using the event with the greatest intensity.
Any subject with multiple events in one Preferred Term (PT) was counted only once for that PT, using the event with the greatest intensity.

Cross Reference: Listing 16.2.7

Table 14.3.1.3 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Greatest Intensity (Per Investigator Assessment)

System Organ Class Preferred Term Intensity	Cohort 1 N=3 Number of Subjects (%)	Cohort 1 Number of Events	Cohort 2 N=5 Number of Subjects (%)	Cohort 2 Number of Events	Cohort 3 N=2 Number of Subjects (%)	Cohort 3 Number of Events	Overall N=10 Number of Subjects (%)	Overall Number of Events	Siblings N=4 Number of Subjects (%)	Siblings Number of Events
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
NAEVUS FLAMMEUS	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
GASTROINTESTINAL DISORDERS	0 (0.0%)	0	1 (20.0%)	1	2 (100%)	2	3 (30.0%)	3	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	1	2 (100%)	2	3 (30.0%)	3	0 (0.0%)	0
SALIVARY HYPERSECRETION	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
UMBILICAL HERNIA	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
VOMITING	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0 (0.0%)	0	1 (20.0%)	1	1 (50.0%)	1	2 (20.0%)	2	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Moderate	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
INJECTION SITE OEDEMA	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
MEDICAL DEVICE COMPLICATION	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Moderate	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
INFECTIONS AND INFESTATIONS	2 (66.7%)	2	4 (80.0%)	7	1 (50.0%)	1	7 (70.0%)	10	1 (25.0%)	2
Mild	1 (33.3%)	1	0 (0.0%)	2	0 (0.0%)	0	1 (10.0%)	3	0 (0.0%)	0
Moderate	0 (0.0%)	0	3 (60.0%)	3	0 (0.0%)	0	3 (30.0%)	3	1 (25.0%)	2

Note: Adverse events summarized include both serious and nonserious adverse events.
Treatment Emergent AEs are AEs that occurred after administration of study drug.
Percentages are based on the total number of subjects in each treatment group (N).
Any subject with multiple events in one System Organ Class (SOC) was counted only once for that SOC, using the event with the greatest intensity.
Any subject with multiple events in one Preferred Term (PT) was counted only once for that PT, using the event with the greatest intensity.

Cross Reference: Listing 16.2.7

Table 14.3.1.3 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Greatest Intensity (Per Investigator Assessment)

System Organ Class Preferred Term Intensity	Cohort 1 N=3 Number of Subjects (%)	 Number of Events	Cohort 2 N=5 Number of Subjects (%)	 Number of Events	Cohort 3 N=2 Number of Subjects (%)	 Number of Events	Overall N=10 Number of Subjects (%)	 Number of Events	Siblings N=4 Number of Subjects (%)	 Number of Events
Severe	1 (33.3%)	1	1 (20.0%)	2	1 (50.0%)	1	3 (30.0%)	4	0 (0.0%)	0
BRONCHIOLITIS	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Severe	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
BRONCHOPNEUMONIA	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Severe	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
LOWER RESPIRATORY TRACT INFECTION	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Severe	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
OTITIS MEDIA	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Moderate	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
PHARYNGITIS	0 (0.0%)	0	1 (20.0%)	2	0 (0.0%)	0	1 (10.0%)	2	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	2	0 (0.0%)	0	1 (10.0%)	2	0 (0.0%)	0
PYELONEPHRITIS	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Moderate	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
RESPIRATORY SYNCYTIAL VIRUS INFECTION	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Severe	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
UPPER RESPIRATORY TRACT INFECTION	1 (33.3%)	1	1 (20.0%)	1	0 (0.0%)	0	2 (20.0%)	2	1 (25.0%)	1
Mild	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Moderate	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	1 (25.0%)	1
VIRAL INFECTION	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (25.0%)	1
Moderate	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (25.0%)	1
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
PROCEDURAL SITE REACTION	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0

Note: Adverse events summarized include both serious and nonserious adverse events.
Treatment Emergent AEs are AEs that occurred after administration of study drug.
Percentages are based on the total number of subjects in each treatment group (N).
Any subject with multiple events in one System Organ Class (SOC) was counted only once for that SOC, using the event with the greatest intensity.
Any subject with multiple events in one Preferred Term (PT) was counted only once for that PT, using the event with the greatest intensity.

Cross Reference: Listing 16.2.7

Table 14.3.1.3 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Greatest Intensity (Per Investigator Assessment)

System Organ Class Preferred Term Intensity	Cohort 1 N=3 Number of Subjects (%)	Cohort 1 N=3 Number of Events	Cohort 2 N=5 Number of Subjects (%)	Cohort 2 N=5 Number of Events	Cohort 3 N=2 Number of Subjects (%)	Cohort 3 N=2 Number of Events	Overall N=10 Number of Subjects (%)	Overall N=10 Number of Events	Siblings N=4 Number of Subjects (%)	Siblings N=4 Number of Events
INVESTIGATIONS	3 (100%)	34	5 (100%)	45	2 (100%)	34	10 (100%)	113	0 (0.0%)	0
Mild	3 (100%)	34	5 (100%)	45	2 (100%)	34	10 (100%)	113	0 (0.0%)	0
ALANINE AMINOTRANSFERASE INCREASED	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
ALBUMIN URINE PRESENT	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
ASPARTATE AMINOTRANSFERASE INCREASED	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
BASOPHIL COUNT DECREASED	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
BASOPHIL COUNT INCREASED	0 (0.0%)	0	4 (80.0%)	6	1 (50.0%)	1	5 (50.0%)	7	0 (0.0%)	0
Mild	0 (0.0%)	0	4 (80.0%)	6	1 (50.0%)	1	5 (50.0%)	7	0 (0.0%)	0
BLOOD ALBUMIN DECREASED	0 (0.0%)	0	1 (20.0%)	2	0 (0.0%)	0	1 (10.0%)	2	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	2	0 (0.0%)	0	1 (10.0%)	2	0 (0.0%)	0
BLOOD ALKALINE PHOSPHATASE INCREASED	0 (0.0%)	0	2 (40.0%)	2	1 (50.0%)	1	3 (30.0%)	3	0 (0.0%)	0
Mild	0 (0.0%)	0	2 (40.0%)	2	1 (50.0%)	1	3 (30.0%)	3	0 (0.0%)	0
BLOOD BICARBONATE INCREASED	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
BLOOD BILIRUBIN INCREASED	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
BLOOD CHLORIDE INCREASED	0 (0.0%)	0	3 (60.0%)	3	0 (0.0%)	0	3 (30.0%)	3	0 (0.0%)	0
Mild	0 (0.0%)	0	3 (60.0%)	3	0 (0.0%)	0	3 (30.0%)	3	0 (0.0%)	0
BLOOD CREATININE DECREASED	2 (66.7%)	3	4 (80.0%)	4	0 (0.0%)	0	6 (60.0%)	7	0 (0.0%)	0
Mild	2 (66.7%)	3	4 (80.0%)	4	0 (0.0%)	0	6 (60.0%)	7	0 (0.0%)	0
BLOOD CREATININE INCREASED	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
BLOOD GLUCOSE INCREASED	1 (33.3%)	1	2 (40.0%)	2	0 (0.0%)	0	3 (30.0%)	3	0 (0.0%)	0

Note: Adverse events summarized include both serious and nonserious adverse events.
Treatment Emergent AEs are AEs that occurred after administration of study drug.
Percentages are based on the total number of subjects in each treatment group (N).
Any subject with multiple events in one System Organ Class (SOC) was counted only once for that SOC, using the event with the greatest intensity.
Any subject with multiple events in one Preferred Term (PT) was counted only once for that PT, using the event with the greatest intensity.

Cross Reference: Listing 16.2.7

Table 14.3.1.3 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Greatest Intensity (Per Investigator Assessment)

System Organ Class Preferred Term Intensity	Cohort 1 N=3 Number of Subjects (%)	Cohort 1 Number of Events	Cohort 2 N=5 Number of Subjects (%)	Cohort 2 Number of Events	Cohort 3 N=2 Number of Subjects (%)	Cohort 3 Number of Events	Overall N=10 Number of Subjects (%)	Overall Number of Events	Siblings N=4 Number of Subjects (%)	Siblings Number of Events
Mild	1 (33.3%)	1	2 (40.0%)	2	0 (0.0%)	0	3 (30.0%)	3	0 (0.0%)	0
BLOOD POTASSIUM INCREASED	1 (33.3%)	1	0 (0.0%)	0	2 (100%)	2	3 (30.0%)	3	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	2 (100%)	2	3 (30.0%)	3	0 (0.0%)	0
BLOOD SODIUM DECREASED	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
BLOOD UREA DECREASED	2 (66.7%)	2	0 (0.0%)	0	1 (50.0%)	1	3 (30.0%)	3	0 (0.0%)	0
Mild	2 (66.7%)	2	0 (0.0%)	0	1 (50.0%)	1	3 (30.0%)	3	0 (0.0%)	0
BLOOD UREA INCREASED	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
BLOOD URINE PRESENT	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
EOSINOPHIL COUNT DECREASED	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
EOSINOPHIL COUNT INCREASED	1 (33.3%)	1	0 (0.0%)	0	1 (50.0%)	2	2 (20.0%)	3	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	1 (50.0%)	2	2 (20.0%)	3	0 (0.0%)	0
HAEMATOCRIT DECREASED	1 (33.3%)	2	1 (20.0%)	1	1 (50.0%)	1	3 (30.0%)	4	0 (0.0%)	0
Mild	1 (33.3%)	2	1 (20.0%)	1	1 (50.0%)	1	3 (30.0%)	4	0 (0.0%)	0
HAEMATOCRIT INCREASED	1 (33.3%)	1	1 (20.0%)	1	1 (50.0%)	1	3 (30.0%)	3	0 (0.0%)	0
Mild	1 (33.3%)	1	1 (20.0%)	1	1 (50.0%)	1	3 (30.0%)	3	0 (0.0%)	0
HAEMOGLOBIN DECREASED	1 (33.3%)	1	1 (20.0%)	1	1 (50.0%)	1	3 (30.0%)	3	0 (0.0%)	0
Mild	1 (33.3%)	1	1 (20.0%)	1	1 (50.0%)	1	3 (30.0%)	3	0 (0.0%)	0
HAEMOGLOBIN INCREASED	1 (33.3%)	1	1 (20.0%)	1	1 (50.0%)	2	3 (30.0%)	4	0 (0.0%)	0
Mild	1 (33.3%)	1	1 (20.0%)	1	1 (50.0%)	2	3 (30.0%)	4	0 (0.0%)	0
LYMPHOCYTE COUNT INCREASED	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
LYMPHOCYTE MORPHOLOGY ABNORMAL	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0

Note: Adverse events summarized include both serious and nonserious adverse events.
Treatment Emergent AEs are AEs that occurred after administration of study drug.
Percentages are based on the total number of subjects in each treatment group (N).
Any subject with multiple events in one System Organ Class (SOC) was counted only once for that SOC, using the event with the greatest intensity.
Any subject with multiple events in one Preferred Term (PT) was counted only once for that PT, using the event with the greatest intensity.

Cross Reference: Listing 16.2.7

Table 14.3.1.3 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Greatest Intensity (Per Investigator Assessment)

System Organ Class Preferred Term Intensity	Cohort 1 N=3 Number of Subjects (%)	 Number of Events	Cohort 2 N=5 Number of Subjects (%)	 Number of Events	Cohort 3 N=2 Number of Subjects (%)	 Number of Events	Overall N=10 Number of Subjects (%)	 Number of Events	Siblings N=4 Number of Subjects (%)	 Number of Events
MEAN CELL HAEMOGLOBIN DECREASED	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
MEAN CELL HAEMOGLOBIN INCREASED	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
MONOCYTE COUNT DECREASED	1 (33.3%)	1	1 (20.0%)	1	1 (50.0%)	1	3 (30.0%)	3	0 (0.0%)	0
Mild	1 (33.3%)	1	1 (20.0%)	1	1 (50.0%)	1	3 (30.0%)	3	0 (0.0%)	0
MONOCYTE COUNT INCREASED	1 (33.3%)	1	4 (80.0%)	5	0 (0.0%)	0	5 (50.0%)	6	0 (0.0%)	0
Mild	1 (33.3%)	1	4 (80.0%)	5	0 (0.0%)	0	5 (50.0%)	6	0 (0.0%)	0
NEUTROPHIL COUNT DECREASED	2 (66.7%)	2	1 (20.0%)	1	0 (0.0%)	0	3 (30.0%)	3	0 (0.0%)	0
Mild	2 (66.7%)	2	1 (20.0%)	1	0 (0.0%)	0	3 (30.0%)	3	0 (0.0%)	0
NEUTROPHIL COUNT INCREASED	0 (0.0%)	0	3 (60.0%)	4	0 (0.0%)	0	3 (30.0%)	4	0 (0.0%)	0
Mild	0 (0.0%)	0	3 (60.0%)	4	0 (0.0%)	0	3 (30.0%)	4	0 (0.0%)	0
OXYGEN SATURATION DECREASED	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
PCO2 INCREASED	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
PH URINE INCREASED	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
PLATELET COUNT INCREASED	1 (33.3%)	2	2 (40.0%)	2	1 (50.0%)	1	4 (40.0%)	5	0 (0.0%)	0
Mild	1 (33.3%)	2	2 (40.0%)	2	1 (50.0%)	1	4 (40.0%)	5	0 (0.0%)	0
PLATELET MORPHOLOGY ABNORMAL	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
PO2 DECREASED	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
PROTEIN TOTAL DECREASED	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
PROTEIN URINE	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0

Note: Adverse events summarized include both serious and nonserious adverse events.
Treatment Emergent AEs are AEs that occurred after administration of study drug.
Percentages are based on the total number of subjects in each treatment group (N).
Any subject with multiple events in one System Organ Class (SOC) was counted only once for that SOC, using the event with the greatest intensity.
Any subject with multiple events in one Preferred Term (PT) was counted only once for that PT, using the event with the greatest intensity.

Cross Reference: Listing 16.2.7

Table 14.3.1.3 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Greatest Intensity (Per Investigator Assessment)

System Organ Class Preferred Term Intensity	Cohort 1 N=3 Number of Subjects (%)	Cohort 1 Number of Events	Cohort 2 N=5 Number of Subjects (%)	Cohort 2 Number of Events	Cohort 3 N=2 Number of Subjects (%)	Cohort 3 Number of Events	Overall N=10 Number of Subjects (%)	Overall Number of Events	Siblings N=4 Number of Subjects (%)	Siblings Number of Events
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
RED BLOOD CELL COUNT INCREASED	2 (66.7%)	2	1 (20.0%)	1	0 (0.0%)	0	3 (30.0%)	3	0 (0.0%)	0
Mild	2 (66.7%)	2	1 (20.0%)	1	0 (0.0%)	0	3 (30.0%)	3	0 (0.0%)	0
RED BLOOD CELL ELLIPTOCYTES PRESENT	1 (33.3%)	1	0 (0.0%)	0	1 (50.0%)	1	2 (20.0%)	2	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	1 (50.0%)	1	2 (20.0%)	2	0 (0.0%)	0
RED BLOOD CELL MACROCYTES PRESENT	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	2	1 (10.0%)	2	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	2	1 (10.0%)	2	0 (0.0%)	0
RED BLOOD CELL MICROCYTES PRESENT	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
RED BLOOD CELL SCHISTOCYTES PRESENT	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
RED BLOOD CELL SPHEROCYTES PRESENT	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
SPECIFIC GRAVITY URINE DECREASED	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
SPECIFIC GRAVITY URINE INCREASED	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
URINE ANALYSIS ABNORMAL	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	3	1 (10.0%)	3	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	3	1 (10.0%)	3	0 (0.0%)	0
URINE LEUKOCYTE ESTERASE POSITIVE	1 (33.3%)	1	0 (0.0%)	0	1 (50.0%)	1	2 (20.0%)	2	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	1 (50.0%)	1	2 (20.0%)	2	0 (0.0%)	0
WHITE BLOOD CELL COUNT INCREASED	0 (0.0%)	0	3 (60.0%)	5	0 (0.0%)	0	3 (30.0%)	5	0 (0.0%)	0
Mild	0 (0.0%)	0	3 (60.0%)	5	0 (0.0%)	0	3 (30.0%)	5	0 (0.0%)	0
METABOLISM AND NUTRITION DISORDERS	1 (33.3%)	3	3 (60.0%)	4	0 (0.0%)	0	4 (40.0%)	7	0 (0.0%)	0
Mild	1 (33.3%)	3	3 (60.0%)	4	0 (0.0%)	0	4 (40.0%)	7	0 (0.0%)	0
HYPERCALCAEMIA	0 (0.0%)	0	1 (20.0%)	2	0 (0.0%)	0	1 (10.0%)	2	0 (0.0%)	0

Note: Adverse events summarized include both serious and nonserious adverse events.
Treatment Emergent AEs are AEs that occurred after administration of study drug.
Percentages are based on the total number of subjects in each treatment group (N).
Any subject with multiple events in one System Organ Class (SOC) was counted only once for that SOC, using the event with the greatest intensity.
Any subject with multiple events in one Preferred Term (PT) was counted only once for that PT, using the event with the greatest intensity.

Cross Reference: Listing 16.2.7

Table 14.3.1.3 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Greatest Intensity (Per Investigator Assessment)

System Organ Class Preferred Term Intensity	Cohort 1 N=3 Number of Subjects (%)	Cohort 1 Number of Events	Cohort 2 N=5 Number of Subjects (%)	Cohort 2 Number of Events	Cohort 3 N=2 Number of Subjects (%)	Cohort 3 Number of Events	Overall N=10 Number of Subjects (%)	Overall Number of Events	Siblings N=4 Number of Subjects (%)	Siblings Number of Events
Mild	0 (0.0%)	0	1 (20.0%)	2	0 (0.0%)	0	1 (10.0%)	2	0 (0.0%)	0
HYPERCHLORAEMIA	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
HYPOALBUMINAEMIA	1 (33.3%)	2	1 (20.0%)	1	0 (0.0%)	0	2 (20.0%)	3	0 (0.0%)	0
Mild	1 (33.3%)	2	1 (20.0%)	1	0 (0.0%)	0	2 (20.0%)	3	0 (0.0%)	0
HYPONATRAEMIA	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	2	1 (10.0%)	2	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	2	1 (10.0%)	2	0 (0.0%)	0
NEONATAL DISORDER	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	2	1 (10.0%)	2	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	2	1 (10.0%)	2	0 (0.0%)	0
PSYCHIATRIC DISORDERS	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
IRRITABILITY	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
RENAL AND URINARY DISORDERS	1 (33.3%)	2	0 (0.0%)	0	1 (50.0%)	1	2 (20.0%)	3	0 (0.0%)	0
Mild	1 (33.3%)	2	0 (0.0%)	0	1 (50.0%)	1	2 (20.0%)	3	0 (0.0%)	0
URINE ABNORMALITY	1 (33.3%)	2	0 (0.0%)	0	1 (50.0%)	1	2 (20.0%)	3	0 (0.0%)	0
Mild	1 (33.3%)	2	0 (0.0%)	0	1 (50.0%)	1	2 (20.0%)	3	0 (0.0%)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0

Note: Adverse events summarized include both serious and nonserious adverse events.
Treatment Emergent AEs are AEs that occurred after administration of study drug.
Percentages are based on the total number of subjects in each treatment group (N).
Any subject with multiple events in one System Organ Class (SOC) was counted only once for that SOC, using the event with the greatest intensity.
Any subject with multiple events in one Preferred Term (PT) was counted only once for that PT, using the event with the greatest intensity.

Cross Reference: Listing 16.2.7

Table 14.3.1.3 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Greatest Intensity (Per Investigator Assessment)

System Organ Class Preferred Term Intensity	Cohort 1 N=3 Number of Subjects (%)	Cohort 1 Number of Events	Cohort 2 N=5 Number of Subjects (%)	Cohort 2 Number of Events	Cohort 3 N=2 Number of Subjects (%)	Cohort 3 Number of Events	Overall N=10 Number of Subjects (%)	Overall Number of Events	Siblings N=4 Number of Subjects (%)	Siblings Number of Events
NASAL CONGESTION	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (33.3%)	1	1 (20.0%)	4	1 (50.0%)	1	3 (30.0%)	6	0 (0.0%)	0
Mild	1 (33.3%)	1	1 (20.0%)	4	1 (50.0%)	1	3 (30.0%)	6	0 (0.0%)	0
DERMATITIS	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
DRY SKIN	0 (0.0%)	0	1 (20.0%)	2	0 (0.0%)	0	1 (10.0%)	2	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	2	0 (0.0%)	0	1 (10.0%)	2	0 (0.0%)	0
HAIR DISORDER	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
HAIR GROWTH ABNORMAL	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
RASH	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Mild	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0

Note: Adverse events summarized include both serious and nonserious adverse events.
Treatment Emergent AEs are AEs that occurred after administration of study drug.
Percentages are based on the total number of subjects in each treatment group (N).
Any subject with multiple events in one System Organ Class (SOC) was counted only once for that SOC, using the event with the greatest intensity.
Any subject with multiple events in one Preferred Term (PT) was counted only once for that PT, using the event with the greatest intensity.

Cross Reference: Listing 16.2.7

Table 14.3.1.4 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Relationship

System Organ Class / Preferred Term / Relationship	Cohort 1 N=3		Cohort 2 N=5		Cohort 3 N=2		Overall N=10		Siblings N=4	
	Number of Subjects (%)	Number of Events	Number of Subjects (%)	Number of Events	Number of Subjects (%)	Number of Events	Number of Subjects (%)	Number of Events	Number of Subjects (%)	Number of Events
All Body Systems	3 (100%)	49	5 (100%)	70	2 (100%)	47	10 (100%)	166	1 (25.0%)	3
Unlikely	2 (66.7%)	30	2 (40.0%)	19	1 (50.0%)	27	5 (50.0%)	76	0 (0.0%)	0
Possibly	1 (33.3%)	13	2 (40.0%)	27	1 (50.0%)	1	4 (40.0%)	41	0 (0.0%)	0
Probably	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2 (66.7%)	6	4 (80.0%)	7	1 (50.0%)	3	7 (70.0%)	16	1 (25.0%)	1
Not Related	1 (33.3%)	1	1 (20.0%)	1	0 (0.0%)	0	2 (20.0%)	2	0 (0.0%)	0
Unlikely	1 (33.3%)	5	0 (0.0%)	3	1 (50.0%)	3	2 (20.0%)	11	0 (0.0%)	0
Possibly	0 (0.0%)	0	3 (60.0%)	3	0 (0.0%)	0	3 (30.0%)	3	0 (0.0%)	0
ANAEMIA	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Not Related	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
EOSINOPHILIA	1 (33.3%)	1	3 (60.0%)	3	0 (0.0%)	0	4 (40.0%)	4	0 (0.0%)	0
Not Related	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Unlikely	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Possibly	0 (0.0%)	0	2 (40.0%)	2	0 (0.0%)	0	2 (20.0%)	2	0 (0.0%)	0
HYPOCHROMASIA	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	2	1 (10.0%)	2	0 (0.0%)	0
Unlikely	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	2	1 (10.0%)	2	0 (0.0%)	0
LYMPHADENOPATHY	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (25.0%)	1
LYMPHOCYTOSIS	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Unlikely	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
MACROCYTOSIS	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Unlikely	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
MONOCYTOSIS	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Possibly	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
POIKILOCYTOSIS	1 (33.3%)	2	0 (0.0%)	0	1 (50.0%)	1	2 (20.0%)	3	0 (0.0%)	0
Unlikely	1 (33.3%)	2	0 (0.0%)	0	1 (50.0%)	1	2 (20.0%)	3	0 (0.0%)	0
RED BLOOD CELL ABNORMALITY	1 (33.3%)	2	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	2	0 (0.0%)	0

Note: Adverse events summarized include both serious and nonserious adverse events.
Treatment Emergent AEs are AEs that occurred after administration of study drug.
Percentages are based on the total number of subjects in each treatment group (N).
Any subject with multiple events in one System Organ Class (SOC) was counted only once for that SOC, using the event related to study drug.
Any subject with multiple events in one Preferred Term (PT) was counted only once for that PT, using the event related to study drug.

Cross Reference: Listing 16.2.7

Table 14.3.1.4 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Relationship

System Organ Class Preferred Term Relationship	Cohort 1 N=3 Number of Subjects (%)	Cohort 1 Number of Events	Cohort 2 N=5 Number of Subjects (%)	Cohort 2 Number of Events	Cohort 3 N=2 Number of Subjects (%)	Cohort 3 Number of Events	Overall N=10 Number of Subjects (%)	Overall Number of Events	Siblings N=4 Number of Subjects (%)	Siblings Number of Events
Unlikely	1 (33.3%)	2	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	2	0 (0.0%)	0
THROMBOCYTOSIS	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Unlikely	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Unlikely	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
NAEVUS FLAMMEUS	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Unlikely	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
GASTROINTESTINAL DISORDERS	0 (0.0%)	0	1 (20.0%)	1	2 (100%)	2	3 (30.0%)	3	0 (0.0%)	0
Not Related	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Unlikely	0 (0.0%)	0	1 (20.0%)	1	1 (50.0%)	1	2 (20.0%)	2	0 (0.0%)	0
SALIVARY HYPERSECRETION	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Not Related	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
UMBILICAL HERNIA	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Unlikely	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
VOMITING	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Unlikely	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0 (0.0%)	0	1 (20.0%)	1	1 (50.0%)	1	2 (20.0%)	2	0 (0.0%)	0
Possibly	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Probably	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
INJECTION SITE OEDEMA	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Probably	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
MEDICAL DEVICE COMPLICATION	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0

Note: Adverse events summarized include both serious and nonserious adverse events.
Treatment Emergent AEs are AEs that occurred after administration of study drug.
Percentages are based on the total number of subjects in each treatment group (N).
Any subject with multiple events in one System Organ Class (SOC) was counted only once for that SOC, using the event related to study drug.
Any subject with multiple events in one Preferred Term (PT) was counted only once for that PT, using the event related to study drug.

Cross Reference: Listing 16.2.7

Table 14.3.1.4 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Relationship

System Organ Class Preferred Term Relationship	Cohort 1 N=3 Number of Subjects (%)	Cohort 1 Number of Events	Cohort 2 N=5 Number of Subjects (%)	Cohort 2 Number of Events	Cohort 3 N=2 Number of Subjects (%)	Cohort 3 Number of Events	Overall N=10 Number of Subjects (%)	Overall Number of Events	Siblings N=4 Number of Subjects (%)	Siblings Number of Events
Possibly	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
INFECTIONS AND INFESTATIONS	2 (66.7%)	2	4 (80.0%)	7	1 (50.0%)	1	7 (70.0%)	10	1 (25.0%)	2
Not Related	1 (33.3%)	1	1 (20.0%)	4	1 (50.0%)	1	3 (30.0%)	6	0 (0.0%)	0
Unlikely	1 (33.3%)	1	3 (60.0%)	3	0 (0.0%)	0	4 (40.0%)	4	0 (0.0%)	0
BRONCHIOLITIS	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Not Related	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
BRONCHOPNEUMONIA	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Unlikely	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
LOWER RESPIRATORY TRACT INFECTION	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Not Related	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
OTITIS MEDIA	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Not Related	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
PHARYNGITIS	0 (0.0%)	0	1 (20.0%)	2	0 (0.0%)	0	1 (10.0%)	2	0 (0.0%)	0
Not Related	0 (0.0%)	0	1 (20.0%)	2	0 (0.0%)	0	1 (10.0%)	2	0 (0.0%)	0
PYELONEPHRITIS	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Unlikely	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
RESPIRATORY SYNCYTIAL VIRUS INFECTION	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Not Related	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
UPPER RESPIRATORY TRACT INFECTION	1 (33.3%)	1	1 (20.0%)	1	0 (0.0%)	0	2 (20.0%)	2	1 (25.0%)	1
Unlikely	1 (33.3%)	1	1 (20.0%)	1	0 (0.0%)	0	2 (20.0%)	2	0 (0.0%)	0
VIRAL INFECTION	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (25.0%)	1
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Not Related	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0

Note: Adverse events summarized include both serious and nonserious adverse events.
Treatment Emergent AEs are AEs that occurred after administration of study drug.
Percentages are based on the total number of subjects in each treatment group (N).
Any subject with multiple events in one System Organ Class (SOC) was counted only once for that SOC, using the event related to study drug.
Any subject with multiple events in one Preferred Term (PT) was counted only once for that PT, using the event related to study drug.

Cross Reference: Listing 16.2.7

Table 14.3.1.4 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Relationship

System Organ Class Preferred Term Relationship	Cohort 1 N=3 Number of Subjects (%)	Cohort 1 Number of Events	Cohort 2 N=5 Number of Subjects (%)	Cohort 2 Number of Events	Cohort 3 N=2 Number of Subjects (%)	Cohort 3 Number of Events	Overall N=10 Number of Subjects (%)	Overall Number of Events	Siblings N=4 Number of Subjects (%)	Siblings Number of Events
PROCEDURAL SITE REACTION	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Not Related	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
INVESTIGATIONS	3 (100%)	34	5 (100%)	45	2 (100%)	34	10 (100%)	113	0 (0.0%)	0
Not Related	0 (0.0%)	3	1 (20.0%)	11	1 (50.0%)	13	2 (20.0%)	27	0 (0.0%)	0
Unlikely	2 (66.7%)	21	1 (20.0%)	10	1 (50.0%)	21	4 (40.0%)	52	0 (0.0%)	0
Possibly	1 (33.3%)	10	3 (60.0%)	24	0 (0.0%)	0	4 (40.0%)	34	0 (0.0%)	0
ALANINE AMINOTRANSFERASE INCREASED	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Unlikely	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
ALBUMIN URINE PRESENT	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Unlikely	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
ASPARTATE AMINOTRANSFERASE INCREASED	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Unlikely	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
BASOPHIL COUNT DECREASED	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Possibly	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
BASOPHIL COUNT INCREASED	0 (0.0%)	0	4 (80.0%)	6	1 (50.0%)	1	5 (50.0%)	7	0 (0.0%)	0
Not Related	0 (0.0%)	0	1 (20.0%)	1	1 (50.0%)	1	2 (20.0%)	2	0 (0.0%)	0
Possibly	0 (0.0%)	0	3 (60.0%)	4	0 (0.0%)	0	3 (30.0%)	4	0 (0.0%)	0
BLOOD ALBUMIN DECREASED	0 (0.0%)	0	1 (20.0%)	2	0 (0.0%)	0	1 (10.0%)	2	0 (0.0%)	0
Unlikely	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
BLOOD ALKALINE PHOSPHATASE INCREASED	0 (0.0%)	0	2 (40.0%)	2	1 (50.0%)	1	3 (30.0%)	3	0 (0.0%)	0
Not Related	0 (0.0%)	0	1 (20.0%)	1	1 (50.0%)	1	2 (20.0%)	2	0 (0.0%)	0
Possibly	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
BLOOD BICARBONATE INCREASED	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Unlikely	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
BLOOD BILIRUBIN INCREASED	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Not Related	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0

Note: Adverse events summarized include both serious and nonserious adverse events.
Treatment Emergent AEs are AEs that occurred after administration of study drug.
Percentages are based on the total number of subjects in each treatment group (N).
Any subject with multiple events in one System Organ Class (SOC) was counted only once for that SOC, using the event related to study drug.
Any subject with multiple events in one Preferred Term (PT) was counted only once for that PT, using the event related to study drug.

Cross Reference: Listing 16.2.7

Table 14.3.1.4 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Relationship

System Organ Class Preferred Term Relationship	Cohort 1 N=3 Number of Subjects (%)	Cohort 1 Number of Events	Cohort 2 N=5 Number of Subjects (%)	Cohort 2 Number of Events	Cohort 3 N=2 Number of Subjects (%)	Cohort 3 Number of Events	Overall N=10 Number of Subjects (%)	Overall Number of Events	Siblings N=4 Number of Subjects (%)	Siblings Number of Events
BLOOD CHLORIDE INCREASED	0 (0.0%)	0	3 (60.0%)	3	0 (0.0%)	0	3 (30.0%)	3	0 (0.0%)	0
Not Related	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Possibly	0 (0.0%)	0	2 (40.0%)	2	0 (0.0%)	0	2 (20.0%)	2	0 (0.0%)	0
BLOOD CREATININE DECREASED	2 (66.7%)	3	4 (80.0%)	4	0 (0.0%)	0	6 (60.0%)	7	0 (0.0%)	0
Not Related	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Unlikely	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Possibly	1 (33.3%)	2	3 (60.0%)	3	0 (0.0%)	0	4 (40.0%)	5	0 (0.0%)	0
BLOOD CREATININE INCREASED	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Not Related	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
BLOOD GLUCOSE INCREASED	1 (33.3%)	1	2 (40.0%)	2	0 (0.0%)	0	3 (30.0%)	3	0 (0.0%)	0
Not Related	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Possibly	1 (33.3%)	1	1 (20.0%)	1	0 (0.0%)	0	2 (20.0%)	2	0 (0.0%)	0
BLOOD POTASSIUM INCREASED	1 (33.3%)	1	0 (0.0%)	0	2 (100%)	2	3 (30.0%)	3	0 (0.0%)	0
Not Related	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Unlikely	1 (33.3%)	1	0 (0.0%)	0	1 (50.0%)	1	2 (20.0%)	2	0 (0.0%)	0
BLOOD SODIUM DECREASED	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Unlikely	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
BLOOD UREA DECREASED	2 (66.7%)	2	0 (0.0%)	0	1 (50.0%)	1	3 (30.0%)	3	0 (0.0%)	0
Unlikely	1 (33.3%)	1	0 (0.0%)	0	1 (50.0%)	1	2 (20.0%)	2	0 (0.0%)	0
Possibly	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
BLOOD UREA INCREASED	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Possibly	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
BLOOD URINE PRESENT	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Not Related	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
EOSINOPHIL COUNT DECREASED	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Not Related	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
EOSINOPHIL COUNT INCREASED	1 (33.3%)	1	0 (0.0%)	0	1 (50.0%)	2	2 (20.0%)	3	0 (0.0%)	0

Note: Adverse events summarized include both serious and nonserious adverse events.
Treatment Emergent AEs are AEs that occurred after administration of study drug.
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Any subject with multiple events in one System Organ Class (SOC) was counted only once for that SOC, using the event related to study drug.
Any subject with multiple events in one Preferred Term (PT) was counted only once for that PT, using the event related to study drug.

Cross Reference: Listing 16.2.7

Table 14.3.1.4 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Relationship

System Organ Class Preferred Term Relationship	Cohort 1 N=3 Number of Subjects (%)	Cohort 1 Number of Events	Cohort 2 N=5 Number of Subjects (%)	Cohort 2 Number of Events	Cohort 3 N=2 Number of Subjects (%)	Cohort 3 Number of Events	Overall N=10 Number of Subjects (%)	Overall Number of Events	Siblings N=4 Number of Subjects (%)	Siblings Number of Events
Unlikely	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	2	1 (10.0%)	2	0 (0.0%)	0
Possibly	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
HAEMATOCRIT DECREASED	1 (33.3%)	2	1 (20.0%)	1	1 (50.0%)	1	3 (30.0%)	4	0 (0.0%)	0
Not Related	0 (0.0%)	0	1 (20.0%)	1	1 (50.0%)	1	2 (20.0%)	2	0 (0.0%)	0
Unlikely	1 (33.3%)	2	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	2	0 (0.0%)	0
HAEMATOCRIT INCREASED	1 (33.3%)	1	1 (20.0%)	1	1 (50.0%)	1	3 (30.0%)	3	0 (0.0%)	0
Not Related	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Possibly	1 (33.3%)	1	1 (20.0%)	1	0 (0.0%)	0	2 (20.0%)	2	0 (0.0%)	0
HAEMOGLOBIN DECREASED	1 (33.3%)	1	1 (20.0%)	1	1 (50.0%)	1	3 (30.0%)	3	0 (0.0%)	0
Not Related	0 (0.0%)	0	1 (20.0%)	1	1 (50.0%)	1	2 (20.0%)	2	0 (0.0%)	0
Unlikely	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
HAEMOGLOBIN INCREASED	1 (33.3%)	1	1 (20.0%)	1	1 (50.0%)	2	3 (30.0%)	4	0 (0.0%)	0
Not Related	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	2	1 (10.0%)	2	0 (0.0%)	0
Possibly	1 (33.3%)	1	1 (20.0%)	1	0 (0.0%)	0	2 (20.0%)	2	0 (0.0%)	0
LYMPHOCYTE COUNT INCREASED	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Not Related	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
LYMPHOCYTE MORPHOLOGY ABNORMAL	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Unlikely	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
MEAN CELL HAEMOGLOBIN DECREASED	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Not Related	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
MEAN CELL HAEMOGLOBIN INCREASED	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Unlikely	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
MONOCYTE COUNT DECREASED	1 (33.3%)	1	1 (20.0%)	1	1 (50.0%)	1	3 (30.0%)	3	0 (0.0%)	0
Not Related	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Possibly	1 (33.3%)	1	1 (20.0%)	1	0 (0.0%)	0	2 (20.0%)	2	0 (0.0%)	0
MONOCYTE COUNT INCREASED	1 (33.3%)	1	4 (80.0%)	5	0 (0.0%)	0	5 (50.0%)	6	0 (0.0%)	0
Unlikely	1 (33.3%)	1	1 (20.0%)	2	0 (0.0%)	0	2 (20.0%)	3	0 (0.0%)	0

Note: Adverse events summarized include both serious and nonserious adverse events.
Treatment Emergent AEs are AEs that occurred after administration of study drug.
Percentages are based on the total number of subjects in each treatment group (N).
Any subject with multiple events in one System Organ Class (SOC) was counted only once for that SOC, using the event related to study drug.
Any subject with multiple events in one Preferred Term (PT) was counted only once for that PT, using the event related to study drug.

Cross Reference: Listing 16.2.7

Table 14.3.1.4 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Relationship

System Organ Class Preferred Term Relationship	Cohort 1 N=3 Number of Subjects (%)	Cohort 1 N=3 Number of Events	Cohort 2 N=5 Number of Subjects (%)	Cohort 2 N=5 Number of Events	Cohort 3 N=2 Number of Subjects (%)	Cohort 3 N=2 Number of Events	Overall N=10 Number of Subjects (%)	Overall N=10 Number of Events	Siblings N=4 Number of Subjects (%)	Siblings N=4 Number of Events
Possibly	0 (0.0%)	0	3 (60.0%)	3	0 (0.0%)	0	3 (30.0%)	3	0 (0.0%)	0
NEUTROPHIL COUNT DECREASED	2 (66.7%)	2	1 (20.0%)	1	0 (0.0%)	0	3 (30.0%)	3	0 (0.0%)	0
Not Related	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Unlikely	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Possibly	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
NEUTROPHIL COUNT INCREASED	0 (0.0%)	0	3 (60.0%)	4	0 (0.0%)	0	3 (30.0%)	4	0 (0.0%)	0
Unlikely	0 (0.0%)	0	2 (40.0%)	2	0 (0.0%)	0	2 (20.0%)	2	0 (0.0%)	0
Possibly	0 (0.0%)	0	1 (20.0%)	2	0 (0.0%)	0	1 (10.0%)	2	0 (0.0%)	0
OXYGEN SATURATION DECREASED	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Unlikely	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
PCO2 INCREASED	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Unlikely	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
PH URINE INCREASED	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Unlikely	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
PLATELET COUNT INCREASED	1 (33.3%)	2	2 (40.0%)	2	1 (50.0%)	1	4 (40.0%)	5	0 (0.0%)	0
Not Related	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Unlikely	1 (33.3%)	2	1 (20.0%)	1	1 (50.0%)	1	3 (30.0%)	4	0 (0.0%)	0
PLATELET MORPHOLOGY ABNORMAL	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Unlikely	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
PO2 DECREASED	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Unlikely	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
PROTEIN TOTAL DECREASED	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Unlikely	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
PROTEIN URINE	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Not Related	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
RED BLOOD CELL COUNT INCREASED	2 (66.7%)	2	1 (20.0%)	1	0 (0.0%)	0	3 (30.0%)	3	0 (0.0%)	0
Not Related	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0

Note: Adverse events summarized include both serious and nonserious adverse events.
Treatment Emergent AEs are AEs that occurred after administration of study drug.
Percentages are based on the total number of subjects in each treatment group (N).
Any subject with multiple events in one System Organ Class (SOC) was counted only once for that SOC, using the event related to study drug.
Any subject with multiple events in one Preferred Term (PT) was counted only once for that PT, using the event related to study drug.

Cross Reference: Listing 16.2.7

Table 14.3.1.4 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Relationship

System Organ Class Preferred Term Relationship	Cohort 1 N=3 Number of Subjects (%)	Cohort 1 Number of Events	Cohort 2 N=5 Number of Subjects (%)	Cohort 2 Number of Events	Cohort 3 N=2 Number of Subjects (%)	Cohort 3 Number of Events	Overall N=10 Number of Subjects (%)	Overall Number of Events	Siblings N=4 Number of Subjects (%)	Siblings Number of Events
Possibly	1 (33.3%)	1	1 (20.0%)	1	0 (0.0%)	0	2 (20.0%)	2	0 (0.0%)	0
RED BLOOD CELL ELLIPTOCYTES PRESENT	1 (33.3%)	1	0 (0.0%)	0	1 (50.0%)	1	2 (20.0%)	2	0 (0.0%)	0
Unlikely	1 (33.3%)	1	0 (0.0%)	0	1 (50.0%)	1	2 (20.0%)	2	0 (0.0%)	0
RED BLOOD CELL MACROCYTES PRESENT	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	2	1 (10.0%)	2	0 (0.0%)	0
Unlikely	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	2	1 (10.0%)	2	0 (0.0%)	0
RED BLOOD CELL MICROCYTES PRESENT	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Unlikely	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
RED BLOOD CELL SCHISTOCYTES PRESENT	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Unlikely	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
RED BLOOD CELL SPHEROCYTES PRESENT	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Unlikely	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
SPECIFIC GRAVITY URINE DECREASED	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Unlikely	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
SPECIFIC GRAVITY URINE INCREASED	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Unlikely	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
URINE ANALYSIS ABNORMAL	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	3	1 (10.0%)	3	0 (0.0%)	0
Unlikely	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	3	1 (10.0%)	3	0 (0.0%)	0
URINE LEUKOCYTE ESTERASE POSITIVE	1 (33.3%)	1	0 (0.0%)	0	1 (50.0%)	1	2 (20.0%)	2	0 (0.0%)	0
Unlikely	1 (33.3%)	1	0 (0.0%)	0	1 (50.0%)	1	2 (20.0%)	2	0 (0.0%)	0
WHITE BLOOD CELL COUNT INCREASED	0 (0.0%)	0	3 (60.0%)	5	0 (0.0%)	0	3 (30.0%)	5	0 (0.0%)	0
Unlikely	0 (0.0%)	0	1 (20.0%)	3	0 (0.0%)	0	1 (10.0%)	3	0 (0.0%)	0
Possibly	0 (0.0%)	0	2 (40.0%)	2	0 (0.0%)	0	2 (20.0%)	2	0 (0.0%)	0
METABOLISM AND NUTRITION DISORDERS	1 (33.3%)	3	3 (60.0%)	4	0 (0.0%)	0	4 (40.0%)	7	0 (0.0%)	0
Not Related	0 (0.0%)	0	1 (20.0%)	2	0 (0.0%)	0	1 (10.0%)	2	0 (0.0%)	0
Unlikely	0 (0.0%)	0	2 (40.0%)	2	0 (0.0%)	0	2 (20.0%)	2	0 (0.0%)	0
Possibly	1 (33.3%)	3	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	3	0 (0.0%)	0

Note: Adverse events summarized include both serious and nonserious adverse events.
Treatment Emergent AEs are AEs that occurred after administration of study drug.
Percentages are based on the total number of subjects in each treatment group (N).
Any subject with multiple events in one System Organ Class (SOC) was counted only once for that SOC, using the event related to study drug.
Any subject with multiple events in one Preferred Term (PT) was counted only once for that PT, using the event related to study drug.

Cross Reference: Listing 16.2.7

Table 14.3.1.4 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Relationship

System Organ Class Preferred Term Relationship	Cohort 1 N=3 Number of Subjects (%)	Cohort 1 N=3 Number of Events	Cohort 2 N=5 Number of Subjects (%)	Cohort 2 N=5 Number of Events	Cohort 3 N=2 Number of Subjects (%)	Cohort 3 N=2 Number of Events	Overall N=10 Number of Subjects (%)	Overall N=10 Number of Events	Siblings N=4 Number of Subjects (%)	Siblings N=4 Number of Events
HYPERCALCAEMIA	0 (0.0%)	0	1 (20.0%)	2	0 (0.0%)	0	1 (10.0%)	2	0 (0.0%)	0
Not Related	0 (0.0%)	0	1 (20.0%)	2	0 (0.0%)	0	1 (10.0%)	2	0 (0.0%)	0
HYPERCHLORAEMIA	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Unlikely	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
HYPOALBUMINAEMIA	1 (33.3%)	2	1 (20.0%)	1	0 (0.0%)	0	2 (20.0%)	3	0 (0.0%)	0
Unlikely	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Possibly	1 (33.3%)	2	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	2	0 (0.0%)	0
HYPONATRAEMIA	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Possibly	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	2	1 (10.0%)	2	0 (0.0%)	0
Unlikely	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
NEONATAL DISORDER	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	2	1 (10.0%)	2	0 (0.0%)	0
Unlikely	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
PSYCHIATRIC DISORDERS	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Not Related	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
IRRITABILITY	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Not Related	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
RENAL AND URINARY DISORDERS	1 (33.3%)	2	0 (0.0%)	0	1 (50.0%)	1	2 (20.0%)	3	0 (0.0%)	0
Unlikely	1 (33.3%)	2	0 (0.0%)	0	1 (50.0%)	1	2 (20.0%)	3	0 (0.0%)	0
URINE ABNORMALITY	1 (33.3%)	2	0 (0.0%)	0	1 (50.0%)	1	2 (20.0%)	3	0 (0.0%)	0
Unlikely	1 (33.3%)	2	0 (0.0%)	0	1 (50.0%)	1	2 (20.0%)	3	0 (0.0%)	0

Note: Adverse events summarized include both serious and nonserious adverse events.
Treatment Emergent AEs are AEs that occurred after administration of study drug.
Percentages are based on the total number of subjects in each treatment group (N).
Any subject with multiple events in one System Organ Class (SOC) was counted only once for that SOC, using the event related to study drug.
Any subject with multiple events in one Preferred Term (PT) was counted only once for that PT, using the event related to study drug.

Cross Reference: Listing 16.2.7

Table 14.3.1.4 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Relationship

System Organ Class Preferred Term Relationship	Cohort 1 N=3 Number of Subjects (%)	Cohort 1 Number of Events	Cohort 2 N=5 Number of Subjects (%)	Cohort 2 Number of Events	Cohort 3 N=2 Number of Subjects (%)	Cohort 3 Number of Events	Overall N=10 Number of Subjects (%)	Overall Number of Events	Siblings N=4 Number of Subjects (%)	Siblings Number of Events
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Not Related	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
NASAL CONGESTION	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Not Related	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (33.3%)	1	1 (20.0%)	4	1 (50.0%)	1	3 (30.0%)	6	0 (0.0%)	0
Not Related	1 (33.3%)	1	1 (20.0%)	4	1 (50.0%)	1	3 (30.0%)	6	0 (0.0%)	0
DERMATITIS	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Not Related	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
DRY SKIN	0 (0.0%)	0	1 (20.0%)	2	0 (0.0%)	0	1 (10.0%)	2	0 (0.0%)	0
Not Related	0 (0.0%)	0	1 (20.0%)	2	0 (0.0%)	0	1 (10.0%)	2	0 (0.0%)	0
HAIR DISORDER	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Not Related	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
HAIR GROWTH ABNORMAL	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
Not Related	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
RASH	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
Not Related	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0

Note: Adverse events summarized include both serious and nonserious adverse events.
Treatment Emergent AEs are AEs that occurred after administration of study drug.
Percentages are based on the total number of subjects in each treatment group (N).
Any subject with multiple events in one System Organ Class (SOC) was counted only once for that SOC, using the event related to study drug.
Any subject with multiple events in one Preferred Term (PT) was counted only once for that PT, using the event related to study drug.

Cross Reference: Listing 16.2.7

Table 14.3.1.5 Treatment Emergent Adverse Events Leading to Study Withdrawal by System Organ Class and Preferred Term

System Organ Class Preferred Term	Cohort 1 N=3 Number of Subjects (%)	Cohort 1 N=3 Number of Events	Cohort 2 N=5 Number of Subjects (%)	Cohort 2 N=5 Number of Events	Cohort 3 N=2 Number of Subjects (%)	Cohort 3 N=2 Number of Events	Overall N=10 Number of Subjects (%)	Overall N=10 Number of Events	Siblings N=4 Number of Subjects (%)	Siblings N=4 Number of Events
All Body Systems	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0

Note: Adverse events summarized include both serious and nonserious adverse events.
Treatment Emergent AEs are AEs that occurred after administration of study drug.
Percentages are based on the total number of subjects in each treatment group (N).
Any subject with multiple events in one System Organ Class (SOC) was counted only once for that SOC.
Any subject with multiple events in one Preferred Term (PT) was counted only once for that PT.

Cross Reference: Listing 16.2.7

Table 14.3.1.6 Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term

System Organ Class Preferred Term	Cohort 1 N=3 Number of Subjects (%)	Cohort 1 N=3 Number of Events	Cohort 2 N=5 Number of Subjects (%)	Cohort 2 N=5 Number of Events	Cohort 3 N=2 Number of Subjects (%)	Cohort 3 N=2 Number of Events	Overall N=10 Number of Subjects (%)	Overall N=10 Number of Events	Siblings N=4 Number of Subjects (%)	Siblings N=4 Number of Events
All Body Systems	1 (33.3%)	1	3 (60.0%)	4	1 (50.0%)	1	5 (50.0%)	6	0 (0.0%)	0
INFECTIONS AND INFESTATIONS	1 (33.3%)	1	3 (60.0%)	4	1 (50.0%)	1	5 (50.0%)	6	0 (0.0%)	0
BRONCHIOLITIS	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
BRONCHOPNEUMONIA	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
LOWER RESPIRATORY TRACT INFECTION	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (10.0%)	1	0 (0.0%)	0
PYELONEPHRITIS	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
RESPIRATORY SYNCYTIAL VIRUS INFECTION	1 (33.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0
UPPER RESPIRATORY TRACT INFECTION	0 (0.0%)	0	1 (20.0%)	1	0 (0.0%)	0	1 (10.0%)	1	0 (0.0%)	0

Treatment Emergent SAEs are SAEs that occurred after administration of study drug.
Percentages are based on the total number of subjects in each treatment group (N).
Any subject with multiple events in one System Organ Class (SOC) was counted only once for that SOC.
Any subject with multiple events in one Preferred Term (PT) was counted only once for that PT.

Cross Reference: Listing 16.2.7

Table 14.3.4.1 Summary of Chemistry Results

Sodium (mmol/L)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Baseline	3	136.3	2.52	136.0	134	139						
	Day 1	3	138.0	1.00	138.0	137	139	3	1.7	2.08	1.0	0	4
	Day 16	3	136.0	4.36	138.0	131	139	3	-0.3	4.51	0.0	-5	4
	Day 21	3	133.7	4.16	135.0	129	137	3	-2.7	5.13	-4.0	-7	3
	Month 2	3	136.0	3.61	137.0	132	139	3	-0.3	4.73	-2.0	-4	5
	Month 6	3	137.3	3.79	139.0	133	140	3	1.0	4.00	1.0	-3	5
Cohort 2	Baseline	5	138.6	1.52	138.0	137	141						
	Day 1	5	137.0	3.39	137.0	133	142	5	-1.6	2.07	-2.0	-4	1
	Day 16	5	136.2	0.84	136.0	135	137	5	-2.4	1.52	-2.0	-4	-1
	Day 21	5	135.4	1.14	135.0	134	137	5	-3.2	1.30	-3.0	-5	-2
	Month 2	5	135.8	1.48	136.0	134	138	5	-2.8	1.30	-2.0	-5	-2
	Month 6	5	136.8	1.48	137.0	135	139	5	-1.8	1.64	-1.0	-4	0
Cohort 3	Baseline	2	141.0	0.00	141.0	141	141						
	Day 1	2	138.5	0.71	138.5	138	139	2	0.0	2.83	0.0	-2	2
	Day 16	2	136.5	3.54	136.5	134	139	2	-2.0	0.00	-2.0	-2	-2
	Day 21	2	139.5	0.71	139.5	139	140	2	1.0	4.24	1.0	-2	4
	Month 2	2	137.0	1.41	137.0	136	138	2	-1.5	2.12	-1.5	-3	0
	Month 6	2	139.5	0.71	139.5	139	140	2	1.0	2.83	1.0	-1	3
Overall	Baseline	10	138.4	2.32	138.5	134	141						
	Day 1	10	137.6	2.41	138.0	133	142	10	-0.3	2.45	0.0	-4	4
	Day 16	10	136.2	2.44	136.5	131	139	10	-1.7	2.54	-2.0	-5	4
	Day 21	10	135.7	3.02	135.5	129	140	10	-2.2	3.39	-2.5	-7	4
	Month 2	10	136.1	2.08	136.0	132	139	10	-1.8	2.74	-2.0	-5	5
	Month 6	10	137.5	2.32	138.0	133	140	10	-0.4	2.80	-1.0	-4	5

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline values include only those subjects with both a baseline value and a value for the summarized time period.

Cross Reference: Listing 16.2.8.1

Table 14.3.4.1 Summary of Chemistry Results

Potassium (mmol/L)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Baseline	3	4.2	0.45	4.2	4	5						
	Day 1	3	4.4	0.40	4.3	4	5	3	0.1	0.72	0.5	-1	1
	Day 16	3	4.4	0.78	4.0	4	5	3	0.2	0.95	0.2	-1	1
	Day 21	2	4.7	0.64	4.7	4	5	2	0.4	0.00	0.4	0	0
	Month 2	3	5.2	0.81	5.3	4	6	3	0.9	0.67	0.6	1	2
	Month 6	3	4.3	0.15	4.3	4	4	3	0.0	0.42	-0.1	-0	1
Cohort 2	Baseline	5	4.7	0.68	4.7	4	5						
	Day 1	4	4.7	0.60	4.5	4	6	4	0.2	0.37	0.2	-0	1
	Day 16	5	4.7	0.41	4.5	4	5	5	-0.0	0.61	0.0	-1	1
	Day 21	5	4.8	0.29	4.7	4	5	5	0.0	0.62	0.3	-1	1
	Month 2	5	4.9	0.29	4.9	5	5	5	0.2	0.73	0.3	-1	1
	Month 6	5	4.4	0.32	4.2	4	5	5	-0.3	0.63	0.0	-1	0
Cohort 3	Baseline	1	5.6		5.6	6	6						
	Day 1	1	5.8		5.8	6	6						
	Day 16	2	5.1	0.42	5.1	5	5						
	Day 21	2	4.6	0.28	4.6	4	5						
	Month 2	2	4.9	0.64	4.9	4	5						
	Month 6	2	4.4	0.64	4.4	4	5						
Overall	Baseline	9	4.7	0.68	4.7	4	6						
	Day 1	8	4.7	0.65	4.5	4	6	7	0.2	0.49	0.2	-1	1
	Day 16	10	4.7	0.54	4.6	4	5	8	0.1	0.69	0.1	-1	1
	Day 21	9	4.7	0.33	4.7	4	5	7	0.1	0.53	0.4	-1	1
	Month 2	10	5.0	0.49	5.0	4	6	8	0.5	0.76	0.5	-1	2
	Month 6	10	4.4	0.32	4.3	4	5	8	-0.2	0.56	-0.1	-1	1

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline values include only those subjects with both a baseline value and a value for the summarized time period.

Cross Reference: Listing 16.2.8.1

Table 14.3.4.1 Summary of Chemistry Results

Chloride (mmol/L)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Baseline	3	104.7	2.31	106.0	102	106						
	Day 1	3	106.0	1.73	107.0	104	107	3	1.3	0.58	1.0	1	2
	Day 16	3	103.3	4.04	101.0	101	108	3	-1.3	3.51	-1.0	-5	2
	Day 21	3	101.7	4.73	100.0	98	107	3	-3.0	3.61	-4.0	-6	1
	Month 2	3	104.7	3.79	103.0	102	109	3	0.0	3.61	1.0	-4	3
	Month 6	3	106.0	1.00	106.0	105	107	3	1.3	2.52	1.0	-1	4
Cohort 2	Baseline	5	107.6	3.29	107.0	103	112						
	Day 1	5	108.2	1.92	108.0	106	111	5	0.6	2.70	1.0	-3	4
	Day 16	5	105.0	2.92	104.0	102	109	5	-2.6	5.18	0.0	-10	2
	Day 21	5	103.4	2.61	103.0	100	106	5	-4.2	4.55	-3.0	-12	-1
	Month 2	5	104.6	1.82	105.0	102	107	5	-3.0	3.16	-2.0	-8	0
	Month 6	5	105.6	3.36	105.0	102	111	5	-2.0	5.24	-2.0	-10	4
Cohort 3	Baseline	2	106.5	2.12	106.5	105	108						
	Day 1	2	106.5	0.71	106.5	106	107	2	2.5	2.12	2.5	1	4
	Day 16	2	105.0	1.41	105.0	104	106	2	1.0	0.00	1.0	1	1
	Day 21	2	106.5	2.12	106.5	105	108	2	2.5	3.54	2.5	0	5
	Month 2	1	104.0		104.0	104	104	1	1.0		1.0	1	1
	Month 6	2	106.0	1.41	106.0	105	107	2	2.0	0.00	2.0	2	2
Overall	Baseline	10	106.5	2.88	106.5	102	112						
	Day 1	10	107.2	1.87	107.0	104	111	10	1.2	2.10	1.0	-3	4
	Day 16	10	104.5	2.88	104.0	101	109	10	-1.5	4.09	0.5	-10	2
	Day 21	10	103.5	3.41	104.0	98	108	10	-2.5	4.55	-2.0	-12	5
	Month 2	9	104.6	2.30	104.0	102	109	9	-1.6	3.36	-1.0	-8	3
	Month 6	10	105.8	2.35	105.5	102	111	10	-0.2	4.16	1.0	-10	4

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline values include only those subjects with both a baseline value and a value for the summarized time period.

Cross Reference: Listing 16.2.8.1

Table 14.3.4.1 Summary of Chemistry Results

Calcium (mmol/L)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Baseline	3	2.5	0.35	2.4	2	3						
	Day 1	3	2.5	0.06	2.5	2	3	3	0.0	0.30	0.1	-0	0
	Day 16	3	2.6	0.06	2.5	3	3	3	0.0	0.29	0.1	-0	0
	Day 21	3	2.6	0.10	2.6	3	3	3	0.1	0.25	0.2	-0	0
	Month 2	3	2.5	0.09	2.6	2	3	3	0.0	0.32	0.2	-0	0
	Month 6	3	2.5	0.08	2.5	2	3	3	0.0	0.27	0.1	-0	0
Cohort 2	Baseline	5	2.5	0.22	2.6	2	3						
	Day 1	5	2.5	0.11	2.5	2	3	5	-0.1	0.13	-0.1	-0	0
	Day 16	5	2.6	0.04	2.6	3	3	5	0.0	0.21	-0.0	-0	0
	Day 21	5	2.6	0.11	2.6	2	3	5	0.1	0.20	0.0	-0	0
	Month 2	5	2.5	0.05	2.5	2	3	5	0.0	0.24	0.0	-0	0
	Month 6	5	2.5	0.05	2.5	2	3	5	0.0	0.22	0.0	-0	0
Cohort 3	Baseline	2	2.5	0.13	2.5	2	3						
	Day 1	2	2.6	0.12	2.6	3	3	2	0.2	0.08	0.2	0	0
	Day 16	1	2.4		2.4	2	2	1	0.0		0.0	0	0
	Day 21	2	2.5	0.00	2.5	3	3	2	0.1	0.04	0.1	0	0
	Month 2	2	2.6	0.00	2.6	3	3	2	0.2	0.04	0.2	0	0
	Month 6	2	2.6	0.01	2.6	3	3	2	0.2	0.04	0.2	0	0
Overall	Baseline	10	2.5	0.22	2.5	2	3						
	Day 1	10	2.5	0.10	2.5	2	3	10	0.0	0.19	0.0	-0	0
	Day 16	9	2.5	0.06	2.5	2	3	9	0.0	0.21	0.0	-0	0
	Day 21	10	2.6	0.10	2.6	2	3	10	0.1	0.18	0.1	-0	0
	Month 2	10	2.6	0.06	2.6	2	3	10	0.1	0.23	0.1	-0	0
	Month 6	10	2.6	0.06	2.6	2	3	10	0.1	0.21	0.1	-0	0

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline values include only those subjects with both a baseline value and a value for the summarized time period.

Cross Reference: Listing 16.2.8.1

Table 14.3.4.1 Summary of Chemistry Results

BUN (mg/dL)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Baseline	3	13.0	9.54	12.0	4	23						
	Day 1	3	9.7	6.51	10.0	3	16	3	-3.3	3.21	-2.0	-7	-1
	Day 16	3	6.3	0.58	6.0	6	7	3	-6.7	10.02	-6.0	-17	3
	Day 21	3	8.0	1.00	8.0	7	9	3	-5.0	8.54	-4.0	-14	3
	Month 2	2	6.5	3.54	6.5	4	9	2	-7.0	16.97	-7.0	-19	5
	Month 6	3	6.7	3.79	5.0	4	11	3	-6.3	13.01	-7.0	-19	7
Cohort 2	Baseline	5	10.8	8.32	7.0	1	21						
	Day 1	5	8.5	6.22	7.0	2	15	5	-2.3	2.61	-3.0	-6	0
	Day 16	5	10.0	6.40	9.0	3	18	5	-0.8	3.31	0.0	-6	2
	Day 21	4	12.8	7.41	13.5	3	21	4	1.0	6.37	2.4	-8	7
	Month 2	5	10.6	4.67	9.0	6	18	5	-0.2	5.21	1.0	-9	5
	Month 6	5	18.0	9.62	17.0	8	31	5	7.2	10.10	3.0	-1	24
Cohort 3	Baseline	2	4.0	0.00	4.0	4	4						
	Day 1	2	4.0	0.00	4.0	4	4	2	-0.5	0.71	-0.5	-1	0
	Day 16	2	9.0	4.24	9.0	6	12	2	4.5	3.54	4.5	2	7
	Day 21	2	10.0	2.83	10.0	8	12	2	5.5	2.12	5.5	4	7
	Month 2	2	7.5	3.54	7.5	5	10	2	3.0	2.83	3.0	1	5
	Month 6	2	8.0	1.41	8.0	7	9	2	3.5	2.12	3.5	2	5
Overall	Baseline	10	10.1	7.90	7.0	1	23						
	Day 1	10	8.0	5.59	5.5	2	16	10	-2.3	2.54	-1.5	-7	0
	Day 16	10	8.7	4.81	6.5	3	18	10	-1.5	6.76	0.9	-17	7
	Day 21	9	10.6	5.17	9.0	3	21	9	-0.0	7.17	3.0	-14	7
	Month 2	9	9.0	4.21	9.0	4	18	9	-1.0	8.00	1.0	-19	5
	Month 6	10	12.6	8.78	9.5	4	31	10	2.4	11.03	2.5	-19	24

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline values include only those subjects with both a baseline value and a value for the summarized time period.

Cross Reference: Listing 16.2.8.1

Table 14.3.4.1 Summary of Chemistry Results

Glucose (mg/dL)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Baseline	3	70.7	16.29	78.0	52	82						
	Day 1	3	89.0	12.29	94.0	75	98	3	18.3	5.69	20.0	12	23
	Day 16	3	96.7	3.51	97.0	93	100	3	26.0	19.47	19.0	11	48
	Day 21	3	91.0	9.54	86.0	85	102	3	20.3	25.74	7.0	4	50
	Month 2	3	95.0	5.57	96.0	89	100	3	24.3	17.39	18.0	11	44
	Month 6	3	90.3	9.29	93.0	80	98	3	19.7	21.50	20.0	-2	41
Cohort 2	Baseline	4	86.9	2.90	86.0	85	91						
	Day 1	4	87.7	13.51	85.0	76	105	4	0.8	14.69	0.1	-15	18
	Day 16	4	95.7	14.58	95.5	79	113	4	8.8	12.67	9.6	-6	22
	Day 21	4	82.0	2.57	82.0	79	85	4	-5.0	2.10	-6.0	-6	-2
	Month 2	5	90.8	5.20	90.1	85	99	4	5.3	2.49	5.7	2	8
	Month 6	5	95.2	3.95	97.0	90	99	4	9.6	6.02	11.5	1	14
Cohort 3	Baseline	2	94.1	18.31	94.1	81	107						
	Day 1	2	87.3	1.06	87.3	87	88	2	-5.3	15.13	-5.3	-16	5
	Day 16	2	94.9	11.10	94.9	87	103	2	2.3	27.29	2.3	-17	22
	Day 21	2	94.3	10.96	94.3	87	102	2	1.7	5.23	1.7	-2	5
	Month 2	2	88.5	20.58	88.5	74	103	2	-4.1	4.38	-4.1	-7	-1
	Month 6	1	92.0		92.0	92	92	1	-12.0		-12.0	-12	-12
Overall	Baseline	9	83.1	14.38	84.7	52	107						
	Day 1	9	88.0	10.34	88.0	75	105	9	5.3	14.82	7.2	-16	23
	Day 16	9	95.8	9.94	97.0	79	113	9	13.1	18.68	16.2	-17	48
	Day 21	9	87.7	8.45	85.0	79	102	9	5.0	17.64	-1.8	-6	50
	Month 2	10	91.6	8.51	90.6	74	103	9	9.6	14.75	6.0	-7	44
	Month 6	9	93.2	5.94	93.0	80	99	8	10.7	16.01	11.5	-12	41

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline values include only those subjects with both a baseline value and a value for the summarized time period.

Cross Reference: Listing 16.2.8.1

Table 14.3.4.1 Summary of Chemistry Results

Creatinine (mg/dL)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Baseline	3	0.5	0.08	0.5	0	1						
	Day 1	3	0.4	0.04	0.3	0	0	3	-0.1	0.11	-0.2	-0	0
	Day 16	2	0.2	0.02	0.2	0	0	2	-0.3	0.08	-0.3	-0	-0
	Day 21	3	0.3	0.04	0.3	0	0	3	-0.2	0.10	-0.2	-0	-0
	Month 2	2	0.2	0.01	0.2	0	0	2	-0.3	0.11	-0.3	-0	-0
	Month 6	2	0.2	0.11	0.2	0	0	2	-0.3	0.21	-0.3	-0	-0
Cohort 2	Baseline	5	0.4	0.09	0.4	0	0						
	Day 1	5	0.3	0.09	0.4	0	0	5	-0.1	0.04	-0.1	-0	0
	Day 16	5	0.3	0.04	0.3	0	0	5	-0.1	0.05	-0.1	-0	-0
	Day 21	5	0.3	0.06	0.3	0	0	5	-0.1	0.07	-0.1	-0	-0
	Month 2	5	0.2	0.05	0.2	0	0	5	-0.1	0.07	-0.2	-0	-0
	Month 6	5	0.3	0.09	0.2	0	0	5	-0.1	0.07	-0.2	-0	-0
Cohort 3	Baseline	2	0.4	0.01	0.4	0	0						
	Day 1	2	0.4	0.03	0.4	0	0	2	0.1	0.03	0.1	0	0
	Day 16	2	0.4	0.07	0.4	0	0	2	0.0	0.01	0.0	0	0
	Day 21	2	0.3	0.13	0.3	0	0	2	-0.1	0.07	-0.1	-0	0
	Month 2	2	0.3	0.04	0.3	0	0	2	-0.0	0.02	-0.0	-0	0
	Month 6	2	0.3	0.12	0.3	0	0	2	-0.1	0.06	-0.1	-0	-0
Overall	Baseline	10	0.4	0.08	0.4	0	1						
	Day 1	10	0.4	0.07	0.4	0	0	10	-0.0	0.09	-0.0	-0	0
	Day 16	9	0.3	0.06	0.3	0	0	9	-0.1	0.11	-0.1	-0	0
	Day 21	10	0.3	0.06	0.3	0	0	10	-0.1	0.09	-0.1	-0	0
	Month 2	9	0.3	0.06	0.2	0	0	9	-0.1	0.11	-0.2	-0	0
	Month 6	9	0.3	0.09	0.2	0	0	9	-0.1	0.12	-0.1	-0	-0

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline values include only those subjects with both a baseline value and a value for the summarized time period.

Cross Reference: Listing 16.2.8.1

Table 14.3.4.1 Summary of Chemistry Results

Total Protein (g/L)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Baseline	3	55.0	7.00	55.0	48	62						
	Day 1	3	52.7	2.08	52.0	51	55	3	-2.3	7.77	0.0	-11	4
	Day 16	3	54.3	1.53	54.0	53	56	3	-0.7	6.66	1.0	-8	5
	Day 21	3	59.0	3.61	58.0	56	63	3	4.0	3.61	3.0	1	8
	Month 2	3	59.0	1.73	58.0	58	61	3	4.0	5.57	3.0	-1	10
	Month 6	3	63.7	3.51	64.0	60	67	3	8.7	5.77	12.0	2	12
Cohort 2	Baseline	5	52.6	5.46	50.0	48	59						
	Day 1	5	53.8	5.07	52.0	49	61	5	1.2	2.59	2.0	-2	4
	Day 16	5	52.6	2.88	51.0	50	57	5	0.0	5.34	1.0	-8	6
	Day 21	5	51.4	4.28	53.0	44	55	5	-1.2	6.22	-5.0	-6	7
	Month 2	5	56.2	4.09	58.0	49	59	5	3.6	5.90	0.0	-1	11
	Month 6	5	62.2	4.55	63.0	57	67	5	9.6	3.13	9.0	7	15
Cohort 3	Baseline	1	62.0		62.0	62	62						
	Day 1	2	59.5	2.12	59.5	58	61	1	4.0		4.0	4	4
	Day 16	2	52.0	1.41	52.0	51	53	1	-6.0		-6.0	-6	-6
	Day 21	2	53.5	2.12	53.5	52	55	1	-2.0		-2.0	-2	-2
	Month 2	2	60.5	6.36	60.5	56	65	1	8.0		8.0	8	8
	Month 6	2	64.0	1.41	64.0	63	65	1	8.0		8.0	8	8
Overall	Baseline	9	54.4	6.04	55.0	48	62						
	Day 1	10	54.6	4.45	53.5	49	61	9	0.3	4.82	2.0	-11	4
	Day 16	10	53.0	2.31	53.0	50	57	9	-0.9	5.40	1.0	-8	6
	Day 21	10	54.1	4.86	54.0	44	63	9	0.4	5.46	1.0	-6	8
	Month 2	10	57.9	4.01	58.0	49	65	9	4.2	5.21	3.0	-1	11
	Month 6	10	63.0	3.59	63.5	57	67	9	9.1	3.69	9.0	2	15

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline values include only those subjects with both a baseline value and a value for the summarized time period.

Cross Reference: Listing 16.2.8.1

Table 14.3.4.1 Summary of Chemistry Results

Albumin (g/L)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Baseline	3	33.5	1.50	33.6	32	35						
	Day 1	3	32.7	0.61	33.0	32	33	3	-0.8	2.02	-0.5	-3	1
	Day 16	3	33.7	2.41	34.0	31	36	3	0.2	3.36	-1.0	-2	4
	Day 21	3	35.7	5.08	37.0	30	40	3	2.2	4.91	5.0	-4	5
	Month 2	3	36.5	0.50	36.6	36	37	3	3.0	1.00	3.0	2	4
	Month 6	3	42.4	1.18	43.0	41	43	3	8.8	2.57	9.5	6	11
Cohort 2	Baseline	5	33.5	2.44	34.0	30	36						
	Day 1	5	32.4	3.37	32.9	27	36	5	-1.0	2.05	0.0	-4	1
	Day 16	5	32.4	4.30	34.3	25	36	5	-1.1	2.66	-1.4	-5	2
	Day 21	5	34.3	3.91	35.1	28	39	5	0.8	2.29	0.1	-2	3
	Month 2	5	37.3	3.51	38.8	31	39	5	3.8	2.28	3.6	1	7
	Month 6	5	40.7	2.74	40.6	37	45	5	7.3	2.31	7.0	5	11
Cohort 3	Baseline	2	35.5	2.12	35.5	34	37						
	Day 1	2	34.5	2.12	34.5	33	36	2	-1.5	0.71	-1.5	-2	-1
	Day 16	2	32.0	1.41	32.0	31	33	2	-4.0	1.41	-4.0	-5	-3
	Day 21	2	34.5	3.54	34.5	32	37	2	-1.5	0.71	-1.5	-2	-1
	Month 2	2	35.0	4.24	35.0	32	38	2	-1.0	1.41	-1.0	-2	0
	Month 6	2	40.5	2.12	40.5	39	42	2	4.5	0.71	4.5	4	5
Overall	Baseline	10	33.9	2.09	34.0	30	37						
	Day 1	10	32.9	2.52	33.0	27	36	10	-1.1	1.70	-0.8	-4	1
	Day 16	10	32.7	3.20	33.5	25	36	10	-1.3	2.88	-1.4	-5	4
	Day 21	10	34.8	3.79	35.3	28	40	10	0.8	3.09	-0.1	-4	5
	Month 2	10	36.6	2.89	37.5	31	39	10	2.6	2.54	2.8	-2	7
	Month 6	10	41.2	2.20	41.1	37	45	10	7.2	2.53	6.5	4	11

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Baseline value is the last value taken prior to study drug administration.
Change from baseline values include only those subjects with both a baseline value and a value for the summarized time period.

Cross Reference: Listing 16.2.8.1

Table 14.3.4.1 Summary of Chemistry Results

AST (SGOT) (U/L)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Baseline	3	49.3	27.02	39.0	29	80						
	Day 1	3	32.7	4.73	31.0	29	38	3	-16.7	29.77	-1.0	-51	2
	Day 16	3	30.7	0.58	31.0	30	31	3	-18.7	27.59	-8.0	-50	2
	Day 21	2	41.0	1.41	41.0	40	42	2	-13.5	34.65	-13.5	-38	11
	Month 2	3	55.3	33.50	37.0	35	94	3	6.0	49.00	6.0	-43	55
	Month 6	3	46.3	9.07	45.0	38	56	3	-3.0	28.00	9.0	-35	17
Cohort 2	Baseline	5	30.0	7.52	32.0	18	37						
	Day 1	5	33.4	10.97	37.0	18	46	5	3.4	8.56	7.0	-10	11
	Day 16	5	29.2	6.83	29.0	20	38	5	-0.8	7.19	2.0	-9	6
	Day 21	5	32.6	8.20	28.0	25	42	5	2.6	13.69	-3.0	-9	23
	Month 2	5	30.6	4.98	30.0	26	39	5	0.6	6.91	2.0	-9	10
	Month 6	5	35.2	4.55	35.0	28	40	5	5.2	5.07	5.0	-2	10
Cohort 3	Baseline	1	46.0		46.0	46	46						
	Day 1	1	40.0		40.0	40	40						
	Day 16	1	21.0		21.0	21	21						
	Day 21	2	25.5	3.54	25.5	23	28						
	Month 2	1	34.0		34.0	34	34						
	Month 6	2	42.5	2.12	42.5	41	44						
Overall	Baseline	9	38.2	17.52	35.0	18	80						
	Day 1	9	33.9	8.43	37.0	18	46	8	-4.1	20.07	1.0	-51	11
	Day 16	9	28.8	5.70	30.0	20	38	8	-7.5	18.24	-3.0	-50	6
	Day 21	9	32.9	8.10	28.0	23	42	7	-2.0	19.66	-3.0	-38	23
	Month 2	9	39.2	20.98	34.0	26	94	8	2.6	26.85	2.0	-43	55
	Month 6	10	40.0	7.45	39.0	28	56	8	2.1	16.02	7.0	-35	17

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline values include only those subjects with both a baseline value and a value for the summarized time period.

Cross Reference: Listing 16.2.8.1

Table 14.3.4.1 Summary of Chemistry Results

ALT (SGPT) (U/L)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Baseline	3	16.7	6.66	20.0	9	21						
	Day 1	3	18.3	8.14	22.0	9	24	3	1.7	2.08	1.0	0	4
	Day 16	3	23.7	10.41	27.0	12	32	3	7.0	4.00	7.0	3	11
	Day 21	3	27.3	11.59	33.0	14	35	3	10.7	5.13	12.0	5	15
	Month 2	3	35.0	25.94	27.0	14	64	3	18.3	22.23	6.0	5	44
	Month 6	3	23.0	8.19	25.0	14	30	3	6.3	3.21	5.0	4	10
Cohort 2	Baseline	5	12.8	6.14	14.0	6	20						
	Day 1	5	13.6	4.51	14.0	9	18	5	0.8	3.11	2.0	-3	4
	Day 16	5	13.4	4.28	12.0	9	20	5	0.6	5.22	3.0	-5	6
	Day 21	5	15.4	2.88	16.0	12	19	5	2.6	8.14	5.0	-7	10
	Month 2	5	18.8	11.12	13.0	12	38	5	6.0	11.11	6.0	-5	24
	Month 6	5	18.8	3.96	18.0	13	23	5	6.0	5.48	4.0	1	15
Cohort 3	Baseline	1	23.0		23.0	23	23						
	Day 1	2	23.0	7.07	23.0	18	28						
	Day 16	2	18.5	0.71	18.5	18	19						
	Day 21	2	19.5	2.12	19.5	18	21						
	Month 2	2	26.5	4.95	26.5	23	30						
	Month 6	2	27.5	7.78	27.5	22	33						
Overall	Baseline	9	15.2	6.48	17.0	6	23						
	Day 1	10	16.9	6.66	18.0	9	28	8	1.1	2.64	1.5	-3	4
	Day 16	10	17.5	7.38	16.5	9	32	8	3.0	5.58	3.5	-5	11
	Day 21	10	19.8	7.98	17.5	12	35	8	5.6	7.93	7.5	-7	15
	Month 2	10	25.2	16.20	21.0	12	64	8	10.6	15.89	6.0	-5	44
	Month 6	10	21.8	6.43	22.0	13	33	8	6.1	4.49	4.5	1	15

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline values include only those subjects with both a baseline value and a value for the summarized time period.

Cross Reference: Listing 16.2.8.1

Table 14.3.4.1 Summary of Chemistry Results

Alkaline Phosphatase (U/L)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Baseline	3	134.3	33.08	146.0	97	160						
	Day 1	3	149.3	16.62	147.0	134	167	3	15.0	25.53	21.0	-13	37
	Day 16	3	228.7	34.93	235.0	191	260	3	94.3	5.51	94.0	89	100
	Day 21	3	272.0	43.51	273.0	228	315	3	137.7	15.14	131.0	127	155
	Month 2	3	261.3	114.03	196.0	195	393	3	127.0	94.88	98.0	50	233
	Month 6	3	224.7	111.73	179.0	143	352	3	90.3	88.29	46.0	33	192
Cohort 2	Baseline	5	177.6	41.18	165.0	135	233						
	Day 1	5	207.8	72.43	193.0	124	319	5	30.2	35.09	28.0	-11	86
	Day 16	5	281.0	87.69	294.0	172	368	5	103.4	79.83	135.0	4	195
	Day 21	5	300.8	68.74	286.0	207	390	5	123.2	61.84	107.0	72	225
	Month 2	5	360.0	129.08	385.0	198	541	5	182.4	116.73	160.0	63	376
	Month 6	5	262.6	65.22	272.0	168	349	5	85.0	50.27	81.0	33	142
Cohort 3	Baseline	2	228.0	147.08	228.0	124	332						
	Day 1	2	223.0	141.42	223.0	123	323	1	-9.0		-9.0	-9	-9
	Day 16	2	274.5	160.51	274.5	161	388	1	56.0		56.0	56	56
	Day 21	2	285.5	169.00	285.5	166	405	1	73.0		73.0	73	73
	Month 2	2	314.5	157.68	314.5	203	426	1	94.0		94.0	94	94
	Month 6	2	295.5	140.71	295.5	196	395	1	63.0		63.0	63	63
Overall	Baseline	10	174.7	67.67	154.0	97	332						
	Day 1	10	193.3	74.65	171.5	123	323	9	20.8	30.94	21.0	-13	86
	Day 16	10	264.0	84.57	247.5	161	388	9	95.1	58.55	94.0	4	195
	Day 21	10	289.1	76.62	283.5	166	405	9	122.4	48.60	127.0	72	225
	Month 2	10	321.3	122.88	334.0	195	541	9	154.1	101.45	135.0	50	376
	Month 6	10	257.8	86.95	259.0	143	395	9	84.3	57.30	63.0	33	192

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline values include only those subjects with both a baseline value and a value for the summarized time period.

Cross Reference: Listing 16.2.8.1

Table 14.3.4.2 Summary of Hematology Results

WBC (x10^3/uL)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Baseline	3	10.0	0.55	10.0	10	11						
	Day 1	3	11.1	2.95	10.6	8	14	3	1.1	3.49	0.6	-2	5
	Day 16	3	9.9	1.94	9.4	8	12	3	-0.2	2.33	-1.2	-2	3
	Day 21	3	11.7	3.05	11.0	9	15	3	1.6	3.59	1.0	-2	6
	Month 2	3	9.7	2.22	9.3	8	12	3	-0.3	2.58	-1.3	-2	3
	Month 6	3	9.4	2.32	10.6	7	11	3	-0.7	2.33	0.2	-3	1
Cohort 2	Baseline	5	11.6	5.59	11.0	7	21						
	Day 1	5	17.7	13.71	11.7	7	41	5	6.0	8.40	3.8	-1	20
	Day 16	5	11.4	2.55	12.5	7	13	5	-0.3	4.80	1.4	-8	4
	Day 21	5	11.4	3.33	12.3	6	15	5	-0.2	4.21	1.3	-7	4
	Month 2	5	11.4	2.99	12.5	8	15	5	-0.2	5.11	-0.4	-8	5
	Month 6	5	10.9	3.11	10.1	8	15	5	-0.7	4.14	-0.5	-7	4
Cohort 3	Baseline	2	14.0	3.96	14.0	11	17						
	Day 1	2	13.2	0.28	13.2	13	13	2	-0.8	3.68	-0.8	-3	2
	Day 16	2	8.9	0.42	8.9	9	9	2	-5.1	3.54	-5.1	-8	-3
	Day 21	2	11.3	0.14	11.3	11	11	2	-2.7	4.10	-2.7	-6	0
	Month 2	2	9.1	1.98	9.1	8	11	2	-4.9	1.98	-4.9	-6	-4
	Month 6	2	9.2	0.49	9.2	9	10	2	-4.9	3.46	-4.9	-7	-2
Overall	Baseline	10	11.6	4.22	10.8	7	21						
	Day 1	10	14.8	9.76	12.3	7	41	10	3.2	6.71	1.2	-3	20
	Day 16	10	10.4	2.20	10.3	7	13	10	-1.2	4.13	-1.1	-8	4
	Day 21	10	11.5	2.65	11.3	6	15	10	-0.2	3.89	0.6	-7	6
	Month 2	10	10.4	2.57	9.9	8	15	10	-1.2	4.16	-1.7	-8	5
	Month 6	10	10.1	2.50	9.8	7	15	10	-1.5	3.64	-0.7	-7	4

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline values include only those subjects with both a baseline value and a value for the summarized time period.

Cross Reference: Listing 16.2.8.2

Table 14.3.4.2 Summary of Hematology Results

RBC (x10^6/uL)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Baseline	3	4.8	0.76	4.7	4	6						
	Day 1	3	4.5	0.41	4.5	4	5	3	-0.3	0.73	-0.0	-1	0
	Day 16	3	4.0	0.36	4.0	4	4	3	-0.8	0.76	-0.4	-2	-0
	Day 21	3	4.1	0.24	4.2	4	4	3	-0.7	0.58	-0.5	-1	-0
	Month 2	3	3.6	0.27	3.4	3	4	3	-1.2	0.52	-1.2	-2	-1
	Month 6	3	5.0	0.43	5.2	4	5	3	0.2	0.55	0.3	-0	1
Cohort 2	Baseline	5	4.1	0.79	4.1	3	5						
	Day 1	5	3.9	0.87	4.2	3	5	5	-0.2	0.17	-0.2	-0	0
	Day 16	5	3.5	0.56	3.4	3	4	5	-0.6	0.37	-0.7	-1	0
	Day 21	5	3.4	0.52	3.5	3	4	5	-0.7	0.36	-0.8	-1	-0
	Month 2	5	3.3	0.26	3.4	3	4	5	-0.8	0.85	-0.8	-2	1
	Month 6	5	4.6	0.35	4.9	4	5	5	0.5	0.83	0.4	-0	2
Cohort 3	Baseline	2	5.4	0.10	5.4	5	5						
	Day 1	2	5.2	0.42	5.2	5	5	2	-0.2	0.32	-0.2	-0	0
	Day 16	2	4.0	0.32	4.0	4	4	2	-1.4	0.22	-1.4	-2	-1
	Day 21	2	3.7	0.28	3.7	3	4	2	-1.7	0.18	-1.7	-2	-2
	Month 2	2	3.6	0.18	3.6	4	4	2	-1.7	0.28	-1.7	-2	-2
	Month 6	2	4.5	0.19	4.5	4	5	2	-0.9	0.09	-0.9	-1	-1
Overall	Baseline	10	4.6	0.84	4.6	3	6						
	Day 1	10	4.4	0.80	4.5	3	5	10	-0.2	0.38	-0.2	-1	0
	Day 16	10	3.7	0.51	3.7	3	4	10	-0.8	0.54	-0.7	-2	0
	Day 21	10	3.7	0.50	3.7	3	4	10	-0.9	0.55	-0.9	-2	-0
	Month 2	10	3.4	0.28	3.4	3	4	10	-1.1	0.73	-1.3	-2	1
	Month 6	10	4.7	0.37	4.7	4	5	10	0.1	0.85	0.1	-1	2

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline values include only those subjects with both a baseline value and a value for the summarized time period.

Cross Reference: Listing 16.2.8.2

Table 14.3.4.2 Summary of Hematology Results

Hemoglobin (g/dL)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Baseline	3	17.3	2.51	18.3	14	19						
	Day 1	3	16.0	2.51	14.6	15	19	3	-1.3	2.20	-0.2	-4	0
	Day 16	3	13.4	2.12	12.4	12	16	3	-3.9	2.26	-3.3	-6	-2
	Day 21	3	13.4	1.30	12.7	13	15	3	-3.9	1.92	-4.2	-6	-2
	Month 2	3	10.5	0.20	10.5	10	11	3	-6.8	2.49	-8.0	-8	-4
	Month 6	3	11.3	0.38	11.1	11	12	3	-6.0	2.34	-7.3	-7	-3
Cohort 2	Baseline	5	13.8	2.90	14.7	10	17						
	Day 1	5	13.2	3.28	14.0	9	17	5	-0.6	0.54	-0.7	-1	0
	Day 16	5	11.1	2.13	11.0	9	15	5	-2.7	1.33	-2.9	-4	-1
	Day 21	5	10.7	2.24	11.0	8	13	5	-3.1	0.95	-3.3	-4	-2
	Month 2	5	9.7	0.96	10.0	8	11	5	-4.1	2.78	-4.1	-8	0
	Month 6	5	11.5	1.08	11.3	10	13	5	-2.3	3.22	-2.0	-6	3
Cohort 3	Baseline	2	17.6	0.64	17.6	17	18						
	Day 1	2	16.7	1.84	16.7	15	18	2	-0.9	1.20	-0.9	-2	0
	Day 16	2	12.9	1.56	12.9	12	14	2	-4.7	0.92	-4.7	-5	-4
	Day 21	2	12.0	1.48	12.0	11	13	2	-5.6	0.85	-5.6	-6	-5
	Month 2	2	11.0	0.00	11.0	11	11	2	-6.6	0.64	-6.6	-7	-6
	Month 6	2	11.7	0.49	11.7	11	12	2	-5.9	0.14	-5.9	-6	-6
Overall	Baseline	10	15.6	2.96	16.1	10	19						
	Day 1	10	14.7	3.04	14.7	9	19	10	-0.9	1.21	-0.5	-4	0
	Day 16	10	12.1	2.13	11.9	9	16	10	-3.5	1.64	-3.4	-6	-1
	Day 21	10	11.7	2.10	12.4	8	15	10	-3.9	1.50	-4.0	-6	-2
	Month 2	10	10.2	0.84	10.4	8	11	10	-5.4	2.60	-5.6	-8	0
	Month 6	10	11.5	0.78	11.3	10	13	10	-4.1	3.10	-4.9	-7	3

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline values include only those subjects with both a baseline value and a value for the summarized time period.

Cross Reference: Listing 16.2.8.2

Table 14.3.4.2 Summary of Hematology Results

Hematocrit (%)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Baseline	3	50.1	6.78	53.1	42	55						
	Day 1	3	47.0	8.32	42.6	42	57	3	-3.1	6.54	-0.5	-11	2
	Day 16	3	38.6	5.47	35.9	35	45	3	-11.5	6.01	-9.9	-18	-6
	Day 21	3	38.4	3.42	36.7	36	42	3	-11.7	5.15	-12.5	-16	-6
	Month 2	3	31.8	1.59	30.9	31	34	3	-18.3	5.91	-21.2	-22	-12
	Month 6	3	35.1	2.57	33.7	34	38	3	-14.9	5.56	-16.7	-19	-9
Cohort 2	Baseline	5	40.2	8.59	42.1	28	50						
	Day 1	5	38.6	9.86	42.0	25	50	5	-1.5	1.42	-1.0	-4	-0
	Day 16	5	32.9	6.34	32.8	27	42	5	-7.3	3.60	-8.1	-10	-1
	Day 21	5	31.2	6.09	34.0	24	38	5	-8.9	3.10	-9.3	-12	-5
	Month 2	5	28.7	2.82	29.5	24	31	5	-11.4	8.35	-11.1	-21	2
	Month 6	5	34.1	3.37	34.3	30	38	5	-6.0	9.32	-5.2	-16	8
Cohort 3	Baseline	2	52.6	4.81	52.6	49	56						
	Day 1	2	50.7	7.57	50.7	45	56	2	-2.0	2.76	-2.0	-4	0
	Day 16	2	38.1	5.52	38.1	34	42	2	-14.5	0.71	-14.5	-15	-14
	Day 21	2	34.8	4.53	34.8	32	38	2	-17.8	0.28	-17.8	-18	-18
	Month 2	2	32.5	0.64	32.5	32	33	2	-20.2	5.44	-20.2	-24	-16
	Month 6	2	35.4	2.33	35.4	34	37	2	-17.3	2.47	-17.3	-19	-16
Overall	Baseline	10	45.6	8.92	47.1	28	56						
	Day 1	10	43.5	9.68	43.3	25	57	10	-2.1	3.42	-0.8	-11	2
	Day 16	10	35.7	6.03	35.0	27	45	10	-10.0	4.82	-9.6	-18	-1
	Day 21	10	34.1	5.67	35.4	24	42	10	-11.5	4.76	-11.7	-18	-5
	Month 2	10	30.4	2.69	30.9	24	34	10	-15.2	7.65	-16.2	-24	2
	Month 6	10	34.7	2.73	34.0	30	38	10	-10.9	8.59	-14.3	-19	8

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline values include only those subjects with both a baseline value and a value for the summarized time period.

Cross Reference: Listing 16.2.8.2

Table 14.3.4.2 Summary of Hematology Results

Platelets (x10^3/uL)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Baseline	3	255.0	139.99	187.0	162	416						
	Day 1	3	310.0	168.60	270.0	165	495	3	55.0	45.08	79.0	3	83
	Day 16	3	303.3	120.90	331.0	171	408	3	48.3	104.58	-8.0	-16	169
	Day 21	3	323.7	55.19	308.0	278	385	3	68.7	90.59	91.0	-31	146
	Month 2	3	432.3	93.74	468.0	326	503	3	177.3	148.26	139.0	52	341
	Month 6	3	330.7	78.23	366.0	241	385	3	75.7	118.99	54.0	-31	204
Cohort 2	Baseline	5	350.2	89.85	309.0	279	504						
	Day 1	5	358.4	90.62	391.0	230	454	5	8.2	70.50	24.0	-79	84
	Day 16	5	475.2	96.96	462.0	356	580	5	125.0	65.90	133.0	47	214
	Day 21	5	410.8	105.57	376.0	313	533	5	60.6	67.02	29.0	4	161
	Month 2	5	443.2	154.89	468.0	199	598	5	93.0	139.00	94.0	-110	266
	Month 6	5	350.8	112.03	371.0	209	511	5	0.6	69.22	7.0	-100	92
Cohort 3	Baseline	2	425.5	50.20	425.5	390	461						
	Day 1	2	384.5	84.15	384.5	325	444	2	-41.0	33.94	-41.0	-65	-17
	Day 16	2	363.0	12.73	363.0	354	372	2	-62.5	37.48	-62.5	-89	-36
	Day 21	2	360.0	16.97	360.0	348	372	2	-65.5	33.23	-65.5	-89	-42
	Month 2	2	496.0	7.07	496.0	491	501	2	70.5	43.13	70.5	40	101
	Month 6	2	409.5	50.20	409.5	374	445	2	-16.0	100.41	-16.0	-87	55
Overall	Baseline	10	336.7	110.91	330.5	162	504						
	Day 1	10	349.1	107.65	358.0	165	495	10	12.4	63.54	13.5	-79	84
	Day 16	10	401.2	118.34	390.0	171	580	10	64.5	101.10	61.5	-89	214
	Day 21	10	374.5	85.45	360.0	278	533	10	37.8	83.19	20.5	-89	161
	Month 2	10	450.5	114.98	479.5	199	598	10	113.8	125.22	97.5	-110	341
	Month 6	10	356.5	89.91	371.5	209	511	10	19.8	89.03	13.5	-100	204

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline values include only those subjects with both a baseline value and a value for the summarized time period.

Cross Reference: Listing 16.2.8.2

Table 14.3.4.2 Summary of Hematology Results

Neutrophils (x10^3/uL)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Baseline	3	4.0	2.69	2.6	2	7						
	Day 1	3	3.8	0.68	4.0	3	4	3	-0.2	3.35	1.7	-4	2
	Day 16	3	2.0	0.32	1.9	2	2	3	-2.0	2.37	-0.7	-5	-0
	Day 21	3	2.4	0.47	2.1	2	3	3	-1.6	2.22	-0.5	-4	-0
	Month 2	3	2.6	1.73	2.1	1	4	3	-1.4	3.43	-1.1	-5	2
	Month 6	3	1.7	0.94	1.7	1	3	3	-2.3	1.87	-1.4	-4	-1
Cohort 2	Baseline	5	8.0	8.35	4.4	2	22						
	Day 1	5	14.0	10.78	11.2	4	29	5	6.0	8.24	3.6	-1	20
	Day 16	5	6.9	6.38	4.9	3	18	5	-1.1	2.34	0.0	-4	1
	Day 21	5	7.1	8.44	3.1	2	22	5	-0.9	1.78	-0.8	-4	1
	Month 2	5	3.3	2.10	3.6	1	6	5	-4.7	9.22	-1.7	-21	2
	Month 6	5	7.0	8.47	2.8	2	22	5	-1.0	1.81	-0.1	-4	1
Cohort 3	Baseline	2	6.6	3.32	6.6	4	9						
	Day 1	2	4.9	0.62	4.9	4	5	2	-1.7	3.95	-1.7	-4	1
	Day 16	2	2.3	0.55	2.3	2	3	2	-4.2	3.87	-4.2	-7	-2
	Day 21	2	4.4	0.49	4.4	4	5	2	-2.2	3.81	-2.2	-5	1
	Month 2	2	2.8	0.82	2.8	2	3	2	-3.8	2.50	-3.8	-6	-2
	Month 6	2	2.5	0.30	2.5	2	3	2	-4.1	3.62	-4.1	-7	-2
Overall	Baseline	10	6.5	6.09	4.3	2	22						
	Day 1	10	9.1	8.87	4.8	3	29	10	2.6	6.90	1.4	-4	20
	Day 16	10	4.5	4.93	2.7	2	18	10	-2.0	2.62	-1.1	-7	1
	Day 21	10	5.1	6.05	3.0	2	22	10	-1.4	2.10	-0.7	-5	1
	Month 2	10	3.0	1.68	2.8	1	6	10	-3.5	6.58	-1.9	-21	2
	Month 6	10	4.5	6.25	2.6	1	22	10	-2.0	2.29	-1.5	-7	1

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline values include only those subjects with both a baseline value and a value for the summarized time period.

Cross Reference: Listing 16.2.8.2

Table 14.3.4.2 Summary of Hematology Results

Lymphocytes (x10^3/uL)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Baseline	3	4.3	1.72	5.1	2	5						
	Day 1	3	4.9	1.71	4.4	4	7	3	0.7	1.52	1.3	-1	2
	Day 16	3	5.6	1.83	5.0	4	8	3	1.3	2.24	2.6	-1	3
	Day 21	3	6.8	2.84	6.5	4	10	3	2.5	1.89	1.8	1	5
	Month 2	3	5.2	1.12	5.8	4	6	3	0.9	2.56	0.7	-2	4
	Month 6	3	5.8	1.42	5.4	5	7	3	1.5	2.09	2.2	-1	3
Cohort 2	Baseline	5	16.8	25.30	6.8	3	62						
	Day 1	5	17.9	25.90	5.7	5	64	5	1.0	1.56	1.3	-1	3
	Day 16	5	18.5	28.83	6.2	5	70	5	1.6	4.01	1.5	-3	8
	Day 21	5	19.3	27.26	7.5	6	68	5	2.4	2.41	2.4	-1	6
	Month 2	5	6.5	0.93	6.9	5	8	5	-10.4	25.94	0.2	-57	4
	Month 6	5	18.5	24.96	6.9	5	63	5	1.6	1.56	2.0	-1	4
Cohort 3	Baseline	2	5.2	0.64	5.2	5	6						
	Day 1	2	6.4	1.06	6.4	6	7	2	1.2	1.70	1.2	0	2
	Day 16	2	5.1	0.48	5.1	5	5	2	-0.0	1.12	-0.0	-1	1
	Day 21	2	5.3	0.37	5.3	5	6	2	0.2	0.27	0.2	0	0
	Month 2	2	4.6	0.30	4.6	4	5	2	-0.5	0.94	-0.5	-1	0
	Month 6	2	5.1	0.25	5.1	5	5	2	-0.0	0.38	-0.0	-0	0
Overall	Baseline	10	10.7	18.08	5.3	2	62						
	Day 1	10	11.7	18.48	5.7	4	64	10	1.0	1.40	1.3	-1	3
	Day 16	10	11.9	20.43	5.2	4	70	10	1.2	2.97	1.1	-3	8
	Day 21	10	12.7	19.49	6.7	4	68	10	2.0	2.07	1.8	-1	6
	Month 2	10	5.7	1.16	5.7	4	8	10	-5.0	18.24	0.2	-57	4
	Month 6	10	12.0	18.00	6.0	5	63	10	1.3	1.59	1.5	-1	4

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline values include only those subjects with both a baseline value and a value for the summarized time period.

Cross Reference: Listing 16.2.8.2

Table 14.3.4.2 Summary of Hematology Results

Monocytes (x10^3/uL)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Baseline	3	1.1	0.60	1.3	1	2						
	Day 1	3	1.6	0.40	1.7	1	2	3	0.5	0.43	0.7	-0	1
	Day 16	3	1.5	0.26	1.4	1	2	3	0.4	0.56	0.5	-0	1
	Day 21	3	1.3	0.68	1.4	1	2	3	0.2	0.50	0.1	-0	1
	Month 2	3	1.4	0.43	1.5	1	2	3	0.2	0.17	0.2	0	0
	Month 6	3	0.5	0.42	0.4	0	1	3	-0.6	0.27	-0.7	-1	-0
Cohort 2	Baseline	5	3.5	4.88	0.9	0	12						
	Day 1	5	3.1	4.47	1.3	1	11	5	-0.4	0.96	-0.4	-2	1
	Day 16	5	3.4	3.74	1.7	1	10	5	-0.1	1.66	0.3	-2	2
	Day 21	5	2.3	2.66	1.2	1	7	5	-1.2	2.33	0.0	-5	1
	Month 2	5	0.9	0.34	1.1	1	1	5	-2.6	5.03	0.1	-11	0
	Month 6	5	2.4	3.70	0.8	1	9	5	-1.1	1.54	-0.3	-3	1
Cohort 3	Baseline	2	1.8	1.00	1.8	1	3						
	Day 1	2	1.4	0.04	1.4	1	1	2	-0.4	1.05	-0.4	-1	0
	Day 16	2	0.9	0.44	0.9	1	1	2	-0.9	0.57	-0.9	-1	-1
	Day 21	2	1.0	0.23	1.0	1	1	2	-0.9	0.78	-0.9	-1	-0
	Month 2	2	0.6	0.20	0.6	0	1	2	-1.3	1.20	-1.3	-2	-0
	Month 6	2	0.6	0.25	0.6	0	1	2	-1.2	0.75	-1.2	-2	-1
Overall	Baseline	10	2.5	3.47	1.2	0	12						
	Day 1	10	2.3	3.09	1.4	1	11	10	-0.2	0.88	-0.1	-2	1
	Day 16	10	2.3	2.75	1.4	1	10	10	-0.1	1.24	0.0	-2	2
	Day 21	10	1.7	1.89	1.2	1	7	10	-0.7	1.71	-0.2	-5	1
	Month 2	10	1.0	0.43	1.0	0	2	10	-1.5	3.61	0.1	-11	0
	Month 6	10	1.5	2.66	0.7	0	9	10	-1.0	1.10	-0.7	-3	1

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline values include only those subjects with both a baseline value and a value for the summarized time period.

Cross Reference: Listing 16.2.8.2

Table 14.3.4.2 Summary of Hematology Results

Eosinophils (x10^3/uL)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Baseline	3	0.5	0.10	0.5	0	1						
	Day 1	3	0.7	0.13	0.7	1	1	3	0.2	0.22	0.2	0	1
	Day 16	3	0.7	0.06	0.7	1	1	3	0.2	0.06	0.2	0	0
	Day 21	3	0.8	0.25	0.8	1	1	3	0.3	0.28	0.4	-0	0
	Month 2	3	0.4	0.31	0.4	0	1	3	-0.0	0.23	-0.1	-0	0
	Month 6	3	1.0	1.21	0.3	0	2	3	0.5	1.16	-0.0	-0	2
Cohort 2	Baseline	5	1.0	1.12	0.6	0	3						
	Day 1	5	1.0	1.13	0.5	0	3	5	-0.0	0.28	0.0	-0	0
	Day 16	5	0.8	0.69	0.5	0	2	5	-0.2	0.45	-0.1	-1	0
	Day 21	5	0.9	1.21	0.6	0	3	5	-0.1	0.21	0.0	-0	0
	Month 2	5	0.5	0.22	0.6	0	1	5	-0.5	1.19	0.0	-3	0
	Month 6	5	1.4	2.55	0.3	0	6	5	0.4	1.44	-0.2	-0	3
Cohort 3	Baseline	2	0.3	0.03	0.3	0	0						
	Day 1	2	0.5	0.07	0.5	0	1	2	0.1	0.10	0.1	0	0
	Day 16	2	0.4	0.08	0.4	0	0	2	0.0	0.05	0.0	0	0
	Day 21	2	0.6	0.40	0.6	0	1	2	0.3	0.37	0.3	0	1
	Month 2	2	0.3	0.06	0.3	0	0	2	-0.1	0.09	-0.1	-0	0
	Month 6	2	0.8	0.80	0.8	0	1	2	0.4	0.77	0.4	-0	1
Overall	Baseline	10	0.7	0.81	0.5	0	3						
	Day 1	10	0.8	0.79	0.6	0	3	10	0.1	0.25	0.1	-0	1
	Day 16	10	0.7	0.49	0.6	0	2	10	-0.1	0.36	0.0	-1	0
	Day 21	10	0.8	0.83	0.7	0	3	10	0.1	0.31	0.0	-0	1
	Month 2	10	0.4	0.23	0.4	0	1	10	-0.3	0.83	-0.1	-3	0
	Month 6	10	1.2	1.84	0.3	0	6	10	0.5	1.14	-0.1	-0	3

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline values include only those subjects with both a baseline value and a value for the summarized time period.

Cross Reference: Listing 16.2.8.2

Table 14.3.4.2 Summary of Hematology Results

Basophils (x10^3/uL)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Baseline	3	0.1	0.02	0.1	0	0						
	Day 1	2	0.0	0.01	0.0	0	0	2	-0.1	0.01	-0.1	-0	-0
	Day 16	2	0.1	0.03	0.1	0	0	2	-0.0	0.01	-0.0	-0	-0
	Day 21	2	0.0	0.02	0.0	0	0	2	-0.0	0.00	-0.0	-0	-0
	Month 2	2	0.1	0.15	0.1	0	0	2	0.1	0.13	0.1	-0	0
	Month 6	3	0.1	0.06	0.1	0	0	3	-0.0	0.05	-0.0	-0	0
Cohort 2	Baseline	5	0.2	0.21	0.0	0	1						
	Day 1	4	0.0	0.03	0.0	0	0	4	-0.0	0.06	0.0	-0	0
	Day 16	5	0.1	0.12	0.1	0	0	5	-0.0	0.10	0.0	-0	0
	Day 21	5	0.1	0.09	0.1	0	0	5	-0.0	0.17	0.0	-0	0
	Month 2	5	0.1	0.08	0.0	0	0	5	-0.1	0.13	-0.0	-0	0
	Month 6	5	0.1	0.08	0.1	0	0	5	-0.1	0.14	-0.0	-0	0
Cohort 3	Baseline	1	0.1		0.1	0	0						
	Day 1	1	0.2		0.2	0	0	1	0.1		0.1	0	0
	Day 16	2	0.1	0.01	0.1	0	0	1	0.0		0.0	0	0
	Day 21	2	0.1	0.03	0.1	0	0	1	0.0		0.0	0	0
	Month 2	1	0.1		0.1	0	0	1	0.0		0.0	0	0
	Month 6	1	0.1		0.1	0	0	1	0.0		0.0	0	0
Overall	Baseline	9	0.1	0.15	0.1	0	1						
	Day 1	7	0.1	0.07	0.0	0	0	7	-0.0	0.07	0.0	-0	0
	Day 16	9	0.1	0.09	0.1	0	0	8	-0.0	0.08	-0.0	-0	0
	Day 21	9	0.1	0.07	0.1	0	0	8	-0.0	0.13	-0.0	-0	0
	Month 2	8	0.1	0.09	0.0	0	0	8	-0.0	0.14	-0.0	-0	0
	Month 6	9	0.1	0.06	0.1	0	0	9	-0.1	0.11	-0.0	-0	0

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline values include only those subjects with both a baseline value and a value for the summarized time period.

Cross Reference: Listing 16.2.8.2

Table 14.3.4.5 Summary of Vital Signs

Heart Rate (beats/min)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Baseline	3	145.0	9.54	140.0	139	156						
	Day 0	3	146.3	15.04	154.0	129	156	3	1.3	12.06	0.0	-10	14
	Day 0-Pre-dose	3	147.7	12.74	154.0	133	156	3	2.7	10.26	0.0	-6	14
	Day 0-15min Post	3	146.0	10.00	146.0	136	156	3	1.0	5.57	0.0	-4	7
	Day 0-1hr Post	3	144.0	2.65	145.0	141	146	3	-1.0	12.12	6.0	-15	6
	Day 0-4hr Post	3	139.3	12.66	137.0	128	153	3	-5.7	17.39	-12.0	-19	14
	Day 0-8hr Post	3	143.0	13.45	147.0	128	154	3	-2.0	9.00	-2.0	-11	7
	Day 0-12hr Post	3	147.7	8.39	152.0	138	153	3	2.7	17.93	12.0	-18	14
	Day 0-16hr Post	3	145.3	27.30	158.0	114	164	3	0.3	22.50	8.0	-25	18
	Day 0-20hr Post	3	146.0	22.00	146.0	124	168	3	1.0	14.18	6.0	-15	12
	Day 1	3	142.7	27.15	146.0	114	168	3	-2.3	19.86	6.0	-25	12
	Day 4	3	145.0	12.29	150.0	131	154	3	0.0	12.17	-6.0	-8	14
	Day 4-Pre-dose	3	145.7	11.15	150.0	133	154	3	0.7	11.55	-6.0	-6	14
	Day 4-15min Post	3	142.3	15.50	136.0	131	160	3	-2.7	6.51	-3.0	-9	4
	Day 4-1hr Post	3	152.3	3.79	154.0	148	155	3	7.3	13.28	15.0	-8	15
	Day 4-4hr Post	3	171.3	5.51	171.0	166	177	3	26.3	14.36	32.0	10	37
	Day 4-8hr Post	3	144.7	8.50	145.0	136	153	3	-0.3	17.39	6.0	-20	13
	Day 4-12hr Post	3	136.0	10.82	133.0	127	148	3	-9.0	15.72	-12.0	-23	8
	Day 4-16hr Post	3	135.3	11.93	130.0	127	149	3	-9.7	18.23	-13.0	-26	10
	Day 4-20hr Post	3	150.0	14.11	148.0	137	165	3	5.0	17.58	-2.0	-8	25
	Day 7	3	156.7	16.29	164.0	138	168	3	11.7	12.50	12.0	-1	24
	Day 7-Pre-dose	3	154.7	19.73	164.0	132	168	3	9.7	15.63	12.0	-7	24
	Day 7-15min Post	3	165.3	18.77	155.0	154	187	3	20.3	24.79	16.0	-2	47
	Day 7-1hr Post	3	157.3	1.15	158.0	156	158	3	12.3	9.07	16.0	2	19
	Day 7-4hr Post	3	150.3	20.11	156.0	128	167	3	5.3	29.30	17.0	-28	27
	Day 7-8hr Post	3	145.3	15.70	140.0	133	163	3	0.3	20.98	-7.0	-16	24
	Day 7-12hr Post	3	145.3	5.03	146.0	140	150	3	0.3	6.51	0.0	-6	7
	Day 7-16hr Post	3	155.0	9.54	160.0	144	161	3	10.0	19.08	20.0	-12	22
	Day 7-20hr Post	3	146.3	9.07	150.0	136	153	3	1.3	18.58	10.0	-20	14
	Day 11	3	153.0	17.06	158.0	134	167	3	8.0	16.82	2.0	-5	27
	Day 11-Pre-dose	3	153.0	17.06	158.0	134	167	3	8.0	16.82	2.0	-5	27
	Day 11-15min Post	3	141.7	17.62	147.0	122	156	3	-3.3	12.34	0.0	-17	7
	Day 11-1hr Post	3	150.0	10.00	150.0	140	160	3	5.0	18.73	11.0	-16	20
	Day 11-4hr Post	3	153.0	17.69	150.0	137	172	3	8.0	20.88	-2.0	-6	32

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline includes only those subjects with both a baseline value and a value for then summarized time period.

Cross Reference: Listing 16.2.9

Table 14.3.4.5 Summary of Vital Signs
Heart Rate (beats/min)

		Actual Values						Change From Baseline				
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Day 11-8hr Post	3	157.3	25.79	150.0	136	186	3	12.3	29.19	-3.0	-6	46
	Day 11-12hr Post	3	131.3	20.65	122.0	117	155	3	-13.7	25.54	-22.0	-34	15
	Day 11-16hr Post	3	166.7	17.01	166.0	150	184	3	21.7	19.35	11.0	10	44
	Day 11-20hr Post	3	157.3	16.17	148.0	148	176	3	12.3	22.19	9.0	-8	36
	Day 14	3	163.0	22.61	152.0	148	189	3	18.0	27.62	9.0	-4	49
	Day 14-Pre-dose	3	164.0	21.66	152.0	151	189	3	19.0	27.18	12.0	-4	49
	Day 14-15min Post	3	154.0	5.57	155.0	148	159	3	9.0	6.00	9.0	3	15
	Day 14-1hr Post	3	146.3	11.85	140.0	139	160	3	1.3	18.61	-1.0	-16	21
	Day 14-4hr Post	3	156.3	22.72	160.0	132	177	3	11.3	22.90	4.0	-7	37
	Day 14-8hr Post	3	150.3	22.37	140.0	135	176	3	5.3	28.75	1.0	-21	36
	Day 14-12hr Post	3	162.7	29.50	175.0	129	184	3	17.7	27.02	19.0	-10	44
	Day 14-16hr Post	3	149.3	10.26	152.0	138	158	3	4.3	19.50	13.0	-18	18
	Day 14-20hr Post	3	139.3	5.77	136.0	136	146	3	-5.7	13.58	-4.0	-20	7
	Day 15	3	147.7	10.21	152.0	136	155	3	2.7	19.66	13.0	-20	15
	Day 21	3	151.7	14.05	153.0	137	165	3	6.7	8.74	9.0	-3	14
	Month 2	3	113.3	42.78	119.0	68	153	3	-31.7	51.50	-20.0	-88	13
	Month 4	3	131.3	7.57	128.0	126	140	3	-13.7	15.18	-11.0	-30	0
	Month 6	3	120.0	8.19	118.0	113	129	3	-25.0	16.37	-21.0	-43	-11
Cohort 2	Baseline	5	124.2	20.55	122.0	100	157						
	Day 0	5	141.0	26.15	130.0	114	180	5	16.8	36.01	5.0	-8	80
	Day 0-Pre-dose	5	129.2	13.92	127.0	114	145	5	5.0	21.66	-2.0	-12	42
	Day 0-15min Post	5	141.6	20.28	138.0	114	163	5	17.4	33.02	13.0	-19	60
	Day 0-1hr Post	5	141.6	15.88	139.0	127	168	5	17.4	31.79	10.0	-18	68
	Day 0-4hr Post	5	147.4	18.26	153.0	120	169	5	23.2	30.83	32.0	-16	53
	Day 0-8hr Post	5	148.4	22.98	152.0	111	171	5	24.2	35.28	32.0	-11	71
	Day 0-12hr Post	5	147.8	23.98	152.0	117	174	5	23.6	26.86	17.0	-5	66
	Day 0-16hr Post	5	139.4	14.84	138.0	119	157	5	15.2	25.38	13.0	-7	57
	Day 0-20hr Post	5	150.2	14.10	151.0	134	171	5	26.0	28.75	21.0	-6	71
	Day 1	5	143.6	17.91	143.0	121	171	5	19.4	33.53	22.0	-18	71
	Day 4	5	147.8	10.59	146.0	136	164	5	23.6	30.22	24.0	-21	64
	Day 4-Pre-dose	5	144.0	5.70	142.0	139	153	5	19.8	24.93	22.0	-17	53
	Day 4-15min Post	5	139.6	6.88	141.0	128	146	5	15.4	20.92	21.0	-16	40
	Day 4-1hr Post	5	145.2	8.67	150.0	134	154	5	21.0	28.20	28.0	-23	54

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline includes only those subjects with both a baseline value and a value for then summarized time period.

Cross Reference: Listing 16.2.9

Table 14.3.4.5 Summary of Vital Signs
Heart Rate (beats/min)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 2	Day 4-4hr Post	5	146.4	24.40	142.0	119	185	5	22.2	40.25	22.0	-21	85
	Day 4-8hr Post	5	135.4	14.26	135.0	115	152	5	11.2	24.89	8.0	-12	52
	Day 4-12hr Post	5	137.4	22.58	144.0	112	164	5	13.2	30.74	-4.0	-13	51
	Day 4-16hr Post	4	136.8	11.15	132.5	129	153	4	6.5	7.33	8.5	-4	13
	Day 4-20hr Post	4	129.8	15.78	129.5	111	149	4	-0.5	10.66	-1.0	-11	11
	Day 7	5	155.8	13.57	152.0	142	175	5	31.6	25.77	26.0	7	75
	Day 7-Pre-dose	5	152.0	18.69	152.0	127	175	5	27.8	28.10	20.0	7	75
	Day 7-15min Post	5	145.0	20.04	141.0	119	173	5	20.8	34.80	16.0	-16	73
	Day 7-1hr Post	5	139.0	4.85	140.0	131	144	5	14.8	21.74	18.0	-18	41
	Day 7-4hr Post	5	142.8	10.47	144.0	127	156	5	18.6	16.86	22.0	-1	41
	Day 7-8hr Post	5	128.8	12.24	125.0	115	146	5	4.6	29.43	3.0	-35	46
	Day 7-12hr Post	5	151.2	18.78	152.0	125	173	5	27.0	19.39	20.0	5	52
	Day 7-16hr Post	5	153.2	14.58	147.0	138	176	5	29.0	31.61	25.0	-10	76
	Day 7-20hr Post	5	136.4	17.17	136.0	114	156	5	12.2	33.38	16.0	-31	56
	Day 11	5	158.0	9.03	160.0	143	167	5	33.8	13.54	40.0	10	43
	Day 11-Pre-dose	5	159.4	6.23	160.0	150	167	5	35.2	15.01	40.0	10	50
	Day 11-15min Post	5	140.4	16.71	146.0	116	156	5	16.2	36.13	26.0	-41	56
	Day 11-1hr Post	5	143.4	23.46	133.0	120	175	5	19.2	38.56	8.0	-24	75
	Day 11-4hr Post	5	148.8	32.02	137.0	121	199	5	24.6	46.73	6.0	-20	99
	Day 11-8hr Post	5	141.4	19.98	130.0	124	171	5	17.2	37.95	10.0	-33	71
	Day 11-12hr Post	5	134.4	20.67	129.0	110	166	5	10.2	36.35	9.0	-30	66
	Day 11-16hr Post	5	142.2	14.67	140.0	125	160	5	18.0	30.53	32.0	-32	40
	Day 11-20hr Post	5	137.6	9.89	135.0	131	155	5	13.4	24.52	13.0	-26	35
	Day 14	5	149.8	8.07	150.0	140	160	5	25.6	25.22	28.0	-13	55
	Day 14-Pre-dose	5	149.8	8.07	150.0	140	160	5	25.6	25.22	28.0	-13	55
	Day 14-15min Post	5	144.4	16.99	149.0	121	160	5	20.2	36.01	27.0	-36	59
	Day 14-1hr Post	5	150.8	21.37	146.0	130	183	5	26.6	32.84	35.0	-27	61
	Day 14-4hr Post	5	140.8	13.08	140.0	130	162	5	16.6	21.04	18.0	-15	40
	Day 14-8hr Post	5	147.4	8.44	146.0	140	161	5	23.2	20.98	27.0	-11	41
	Day 14-12hr Post	4	145.8	31.27	138.5	120	186	4	20.5	42.26	27.5	-37	64
	Day 14-16hr Post	5	148.8	16.48	147.0	129	170	5	24.6	35.84	25.0	-28	70
	Day 14-20hr Post	5	148.8	16.42	140.0	132	171	5	24.6	34.95	20.0	-25	71
	Day 15	5	142.2	17.20	136.0	129	170	5	18.0	35.33	16.0	-28	70
	Day 21	5	142.2	14.32	141.0	122	162	5	18.0	29.39	20.0	-16	62

n represents the number of subjects contributing to summary statistics at each visit.
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Cross Reference: Listing 16.2.9

Table 14.3.4.5 Summary of Vital Signs
Heart Rate (beats/min)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 2	Month 2	5	129.6	19.19	117.0	114	153	5	5.4	34.90	-3.0	-41	48
	Month 4	5	130.4	26.06	137.0	99	160	5	6.2	27.47	3.0	-23	48
	Month 6	5	134.8	14.31	140.0	117	153	5	10.6	31.96	18.0	-33	53
Cohort 3	Baseline	2	160.5	6.36	160.5	156	165						
	Day 0	2	144.0	5.66	144.0	140	148	2	-16.5	12.02	-16.5	-25	-8
	Day 0-Pre-dose	2	144.0	5.66	144.0	140	148	2	-16.5	12.02	-16.5	-25	-8
	Day 0-15min Post	2	161.0	12.73	161.0	152	170	2	0.5	6.36	0.5	-4	5
	Day 0-1hr Post	2	148.0	16.97	148.0	136	160	2	-12.5	10.61	-12.5	-20	-5
	Day 0-4hr Post	2	157.5	3.54	157.5	155	160	2	-3.0	9.90	-3.0	-10	4
	Day 0-8hr Post	1	164.0		164.0	164	164	1	8.0		8.0	8	8
	Day 0-12hr Post	2	156.0	8.49	156.0	150	162	2	-4.5	2.12	-4.5	-6	-3
	Day 0-16hr Post	2	168.5	2.12	168.5	167	170	2	8.0	8.49	8.0	2	14
	Day 0-20hr Post	2	162.5	3.54	162.5	160	165	2	2.0	9.90	2.0	-5	9
	Day 0-24hr Post	2	141.0	1.41	141.0	140	142	2	-19.5	7.78	-19.5	-25	-14
	Day 1	2	160.0	7.07	160.0	155	165	2	-0.5	13.44	-0.5	-10	9
	Day 4	2	146.0	19.80	146.0	132	160	2	-14.5	13.44	-14.5	-24	-5
	Day 4-Pre-dose	2	146.0	19.80	146.0	132	160	2	-14.5	13.44	-14.5	-24	-5
	Day 4-15min Post	2	126.0	2.83	126.0	124	128	2	-34.5	9.19	-34.5	-41	-28
	Day 4-1hr Post	2	145.5	14.85	145.5	135	156	2	-15.0	21.21	-15.0	-30	0
	Day 4-4hr Post	2	157.0	21.21	157.0	142	172	2	-3.5	27.58	-3.5	-23	16
	Day 4-8hr Post	2	136.0	22.63	136.0	120	152	2	-24.5	28.99	-24.5	-45	-4
	Day 4-12hr Post	2	148.0	11.31	148.0	140	156	2	-12.5	17.68	-12.5	-25	0
	Day 4-16hr Post	2	153.0	15.56	153.0	142	164	2	-7.5	9.19	-7.5	-14	-1
	Day 4-20hr Post	2	155.5	19.09	155.5	142	169	2	-5.0	12.73	-5.0	-14	4
	Day 4-24hr Post	2	146.5	2.12	146.5	145	148	2	-14.0	8.49	-14.0	-20	-8
	Day 7	2	161.5	0.71	161.5	161	162	2	1.0	7.07	1.0	-4	6
	Day 7-Pre-dose	2	161.5	0.71	161.5	161	162	2	1.0	7.07	1.0	-4	6
	Day 7-15min Post	2	153.0	24.04	153.0	136	170	2	-7.5	17.68	-7.5	-20	5
	Day 7-1hr Post	2	142.5	17.68	142.5	130	155	2	-18.0	11.31	-18.0	-26	-10
	Day 7-4hr Post	2	167.0	4.24	167.0	164	170	2	6.5	10.61	6.5	-1	14
	Day 7-8hr Post	2	143.0	1.41	143.0	142	144	2	-17.5	7.78	-17.5	-23	-12
	Day 7-12hr Post	2	149.0	21.21	149.0	134	164	2	-11.5	14.85	-11.5	-22	-1
	Day 7-16hr Post	2	143.0	1.41	143.0	142	144	2	-17.5	7.78	-17.5	-23	-12

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Cross Reference: Listing 16.2.9

Table 14.3.4.5 Summary of Vital Signs
Heart Rate (beats/min)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 3	Day 7-20hr Post	2	142.0	22.63	142.0	126	158	2	-18.5	16.26	-18.5	-30	-7
	Day 7-24hr Post	2	169.0	1.41	169.0	168	170	2	8.5	4.95	8.5	5	12
	Day 11	2	152.0	15.56	152.0	141	163	2	-8.5	21.92	-8.5	-24	7
	Day 11-Pre-dose	2	152.0	15.56	152.0	141	163	2	-8.5	21.92	-8.5	-24	7
	Day 11-15min Post	2	135.5	13.44	135.5	126	145	2	-25.0	7.07	-25.0	-30	-20
	Day 11-1hr Post	2	135.0	15.56	135.0	124	146	2	-25.5	21.92	-25.5	-41	-10
	Day 11-4hr Post	2	150.0	19.80	150.0	136	164	2	-10.5	13.44	-10.5	-20	-1
	Day 11-8hr Post	2	156.0	33.94	156.0	132	180	2	-4.5	27.58	-4.5	-24	15
	Day 11-12hr Post	2	146.5	2.12	146.5	145	148	2	-14.0	8.49	-14.0	-20	-8
	Day 11-16hr Post	2	151.5	4.95	151.5	148	155	2	-9.0	1.41	-9.0	-10	-8
	Day 11-20hr Post	2	141.0	4.24	141.0	138	144	2	-19.5	10.61	-19.5	-27	-12
	Day 11-24hr Post	2	160.0	11.31	160.0	152	168	2	-0.5	17.68	-0.5	-13	12
	Day 14	2	155.0	9.90	155.0	148	162	2	-5.5	3.54	-5.5	-8	-3
	Day 14-Pre-dose	2	155.0	9.90	155.0	148	162	2	-5.5	3.54	-5.5	-8	-3
	Day 14-15min Post	2	173.0	18.38	173.0	160	186	2	12.5	24.75	12.5	-5	30
	Day 14-1hr Post	2	149.5	14.85	149.5	139	160	2	-11.0	8.49	-11.0	-17	-5
	Day 14-4hr Post	2	136.5	2.12	136.5	135	138	2	-24.0	4.24	-24.0	-27	-21
	Day 14-8hr Post	2	159.5	17.68	159.5	147	172	2	-1.0	11.31	-1.0	-9	7
	Day 14-12hr Post	2	152.5	10.61	152.5	145	160	2	-8.0	16.97	-8.0	-20	4
	Day 14-16hr Post	2	146.0	19.80	146.0	132	160	2	-14.5	26.16	-14.5	-33	4
	Day 14-20hr Post	2	137.0	1.41	137.0	136	138	2	-23.5	4.95	-23.5	-27	-20
	Day 14-24hr Post	2	153.0	7.07	153.0	148	158	2	-7.5	0.71	-7.5	-8	-7
	Day 15	2	151.0	12.73	151.0	142	160	2	-9.5	19.09	-9.5	-23	4
	Day 21	2	163.5	2.12	163.5	162	165	2	3.0	8.49	3.0	-3	9
	Month 2	2	160.0	21.21	160.0	145	175	2	-0.5	14.85	-0.5	-11	10
	Month 4	2	109.5	31.82	109.5	87	132	2	-51.0	25.46	-51.0	-69	-33
	Month 6	2	110.5	13.44	110.5	101	120	2	-50.0	19.80	-50.0	-64	-36
Overall	Baseline	10	137.7	21.14	139.5	100	165						
	Day 0	10	143.2	19.08	144.0	114	180	10	5.5	28.44	-1.5	-25	80
	Day 0-Pre-dose	10	137.7	14.41	141.0	114	156	10	0.0	18.02	-4.0	-25	42
	Day 0-15min Post	10	146.8	16.82	149.0	114	170	10	9.1	23.93	2.5	-19	60
	Day 0-1hr Post	10	143.6	12.34	141.5	127	168	10	5.9	25.67	5.5	-20	68
	Day 0-4hr Post	10	147.0	15.14	153.0	120	169	10	9.3	26.76	1.0	-19	53

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Cross Reference: Listing 16.2.9

Table 14.3.4.5 Summary of Vital Signs
Heart Rate (beats/min)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Overall	Day 0-8hr Post	9	148.3	18.73	152.0	111	171	9	13.7	28.43	7.0	-11	71
	Day 0-12hr Post	10	149.4	17.07	152.0	117	174	10	11.7	23.59	11.0	-18	66
	Day 0-16hr Post	10	147.0	19.99	153.5	114	170	10	9.3	21.29	10.5	-25	57
	Day 0-20hr Post	10	151.4	15.33	152.5	124	171	10	13.7	24.31	10.5	-15	71
	Day 0-24hr Post	2	141.0	1.41	141.0	140	142	2	-19.5	7.78	-19.5	-25	-14
	Day 1	10	146.6	19.03	145.0	114	171	10	8.9	27.02	7.5	-25	71
	Day 4	10	146.6	11.35	148.0	131	164	10	8.9	26.96	4.5	-24	64
	Day 4-Pre-dose	10	144.9	9.30	144.0	132	160	10	7.2	23.09	4.5	-24	53
	Day 4-15min Post	10	137.7	10.72	138.0	124	160	10	0.0	24.74	0.5	-41	40
	Day 4-1hr Post	10	147.4	8.53	150.0	134	156	10	9.7	25.51	15.0	-30	54
	Day 4-4hr Post	10	156.0	21.24	158.0	119	185	10	18.3	31.40	19.0	-23	85
	Day 4-8hr Post	10	138.3	13.52	140.5	115	153	10	0.6	25.27	1.0	-45	52
	Day 4-12hr Post	10	139.1	17.01	142.0	112	164	10	1.4	25.80	-7.0	-25	51
	Day 4-16hr Post	9	139.9	12.97	135.0	127	164	9	-2.0	13.40	-1.0	-26	13
	Day 4-20hr Post	9	142.2	18.25	142.0	111	169	9	0.3	12.48	-2.0	-14	25
	Day 4-24hr Post	2	146.5	2.12	146.5	145	148	2	-14.0	8.49	-14.0	-20	-8
	Day 7	10	157.2	12.09	161.5	138	175	10	19.5	22.66	16.0	-4	75
	Day 7-Pre-dose	10	154.7	16.01	161.5	127	175	10	17.0	23.46	9.5	-7	75
	Day 7-15min Post	10	152.7	20.18	154.0	119	187	10	15.0	29.15	10.5	-20	73
	Day 7-1hr Post	10	145.2	10.84	142.5	130	158	10	7.5	20.60	12.5	-26	41
	Day 7-4hr Post	10	149.9	15.29	151.0	127	170	10	12.2	19.37	15.5	-28	41
	Day 7-8hr Post	10	136.6	13.78	138.0	115	163	10	-1.1	23.83	-6.0	-35	46
	Day 7-12hr Post	10	149.0	14.82	148.0	125	173	10	11.3	22.22	6.0	-22	52
	Day 7-16hr Post	10	151.7	11.69	147.0	138	176	10	14.0	29.71	18.0	-23	76
	Day 7-20hr Post	10	140.5	15.08	143.0	114	158	10	2.8	27.42	1.5	-31	56
	Day 7-24hr Post	2	169.0	1.41	169.0	168	170	2	8.5	4.95	8.5	5	12
	Day 11	10	155.3	11.66	159.0	134	167	10	17.6	22.93	18.5	-24	43
	Day 11-Pre-dose	10	156.0	11.04	159.0	134	167	10	18.3	23.87	18.5	-24	50
	Day 11-15min Post	10	139.8	14.79	145.5	116	156	10	2.1	30.05	3.5	-41	56
	Day 11-1hr Post	10	143.7	17.99	143.0	120	175	10	6.0	33.31	3.0	-41	75
	Day 11-4hr Post	10	150.3	23.93	143.5	121	199	10	12.6	35.96	-1.0	-20	99
	Day 11-8hr Post	10	149.1	22.79	143.0	124	186	10	11.4	31.45	8.5	-33	71
	Day 11-12hr Post	10	135.9	17.84	134.5	110	166	10	-1.8	30.00	-10.0	-34	66
	Day 11-16hr Post	10	151.4	16.95	152.0	125	184	10	13.7	25.37	10.5	-32	44

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Cross Reference: Listing 16.2.9

Table 14.3.4.5 Summary of Vital Signs
Heart Rate (beats/min)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Overall	Day 11-20hr Post	10	144.2	13.69	141.0	131	176	10	6.5	24.02	10.5	-27	36
	Day 11-24hr Post	2	160.0	11.31	160.0	152	168	2	-0.5	17.68	-0.5	-13	12
	Day 14	10	154.8	13.77	151.0	140	189	10	17.1	24.65	14.5	-13	55
	Day 14-Pre-dose	10	155.1	13.64	151.5	140	189	10	17.4	24.56	16.0	-13	55
	Day 14-15min Post	10	153.0	17.41	157.0	121	186	10	15.3	26.09	13.0	-36	59
	Day 14-1hr Post	10	149.2	16.21	143.0	130	183	10	11.5	28.95	10.0	-27	61
	Day 14-4hr Post	10	144.6	16.12	139.0	130	177	10	6.9	24.21	7.0	-27	40
	Day 14-8hr Post	10	150.7	14.17	146.5	135	176	10	13.0	22.68	13.5	-21	41
	Day 14-12hr Post	9	152.9	25.68	155.0	120	186	9	13.2	32.17	19.0	-37	64
	Day 14-16hr Post	10	148.4	13.76	149.5	129	170	10	10.7	31.52	14.5	-33	70
	Day 14-20hr Post	10	143.6	12.58	139.0	132	171	10	5.9	31.90	1.5	-27	71
	Day 14-24hr Post	2	153.0	7.07	153.0	148	158	2	-7.5	0.71	-7.5	-8	-7
	Day 15	10	145.6	13.67	144.5	129	170	10	7.9	28.54	10.0	-28	70
	Day 21	10	149.3	14.50	149.5	122	165	10	11.6	21.36	9.0	-16	62
	Month 2	10	130.8	30.21	132.0	68	175	10	-6.9	38.12	-5.5	-88	48
	Month 4	10	126.5	22.53	130.0	87	160	10	-11.2	31.32	-11.5	-69	48
	Month 6	10	125.5	15.30	122.0	101	153	10	-12.2	34.90	-16.0	-64	53
Siblings	Enrollment	4	93.0	22.77	100.0	60	112						

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline includes only those subjects with both a baseline value and a value for then summarized time period.

Cross Reference: Listing 16.2.9

Table 14.3.4.5 Summary of Vital Signs

Temperature (C)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Baseline	3	36.87	0.231	37.00	36.6	37.0						
	Day 0	3	36.70	0.265	36.80	36.4	36.9	3	-0.17	0.451	-0.20	-0.6	0.3
	Day 0-Pre-dose	3	36.73	0.289	36.90	36.4	36.9	3	-0.13	0.451	-0.10	-0.6	0.3
	Day 0-15min Post	3	36.87	0.208	36.80	36.7	37.1	3	0.00	0.265	0.10	-0.3	0.2
	Day 0-1hr Post	3	36.70	0.557	36.80	36.1	37.2	3	-0.17	0.751	-0.20	-0.9	0.6
	Day 0-4hr Post	3	36.60	0.100	36.60	36.5	36.7	3	-0.27	0.321	-0.40	-0.5	0.1
	Day 0-8hr Post	3	37.10	0.656	37.00	36.5	37.8	3	0.23	0.874	0.00	-0.5	1.2
	Day 0-12hr Post	3	36.77	0.404	36.70	36.4	37.2	3	-0.10	0.624	-0.30	-0.6	0.6
	Day 0-16hr Post	3	36.87	0.503	36.80	36.4	37.4	3	0.00	0.721	-0.20	-0.6	0.8
	Day 0-20hr Post	3	36.87	0.252	36.90	36.6	37.1	3	0.00	0.361	0.10	-0.4	0.3
	Day 1	3	36.93	0.153	36.90	36.8	37.1	3	0.07	0.252	0.10	-0.2	0.3
	Day 4	3	36.67	0.208	36.60	36.5	36.9	3	-0.20	0.436	-0.40	-0.5	0.3
	Day 4-Pre-dose	3	36.67	0.208	36.60	36.5	36.9	3	-0.20	0.436	-0.40	-0.5	0.3
	Day 4-15min Post	3	36.93	0.252	36.90	36.7	37.2	3	0.07	0.473	-0.10	-0.3	0.6
	Day 4-1hr Post	3	36.73	0.289	36.90	36.4	36.9	3	-0.13	0.451	-0.10	-0.6	0.3
	Day 4-4hr Post	3	37.10	0.700	36.80	36.6	37.9	3	0.23	0.929	-0.20	-0.4	1.3
	Day 4-8hr Post	3	36.80	0.100	36.80	36.7	36.9	3	-0.07	0.153	-0.10	-0.2	0.1
	Day 4-12hr Post	3	36.90	0.100	36.90	36.8	37.0	3	0.03	0.252	0.00	-0.2	0.3
	Day 4-16hr Post	3	36.67	0.252	36.70	36.4	36.9	3	-0.20	0.361	-0.10	-0.6	0.1
	Day 4-20hr Post	3	36.80	0.200	36.80	36.6	37.0	3	-0.07	0.115	0.00	-0.2	0.0
	Day 7	3	36.97	0.115	36.90	36.9	37.1	3	0.10	0.200	0.10	-0.1	0.3
	Day 7-Pre-dose	3	36.90	0.000	36.90	36.9	36.9	3	0.03	0.231	-0.10	-0.1	0.3
	Day 7-15min Post	3	36.77	0.451	36.80	36.3	37.2	3	-0.10	0.656	-0.20	-0.7	0.6
	Day 7-1hr Post	3	36.90	0.400	36.90	36.5	37.3	3	0.03	0.462	0.30	-0.5	0.3
	Day 7-4hr Post	3	36.63	0.306	36.70	36.3	36.9	3	-0.23	0.416	-0.10	-0.7	0.1
	Day 7-8hr Post	3	36.93	0.404	37.00	36.5	37.3	3	0.07	0.603	0.00	-0.5	0.7
	Day 7-12hr Post	3	36.60	0.265	36.50	36.4	36.9	3	-0.27	0.493	-0.50	-0.6	0.3
	Day 7-16hr Post	3	36.97	0.451	37.00	36.5	37.4	3	0.10	0.656	0.00	-0.5	0.8
	Day 7-20hr Post	3	36.80	0.173	36.90	36.6	36.9	3	-0.07	0.058	-0.10	-0.1	0.0
	Day 11	3	36.67	0.462	36.40	36.4	37.2	3	-0.20	0.693	-0.60	-0.6	0.6
	Day 11-Pre-dose	3	36.67	0.462	36.40	36.4	37.2	3	-0.20	0.693	-0.60	-0.6	0.6
	Day 11-15min Post	3	36.73	0.153	36.70	36.6	36.9	3	-0.13	0.379	-0.30	-0.4	0.3
	Day 11-1hr Post	3	36.67	0.252	36.70	36.4	36.9	3	-0.20	0.458	-0.30	-0.6	0.3
	Day 11-4hr Post	3	36.80	0.100	36.80	36.7	36.9	3	-0.07	0.321	-0.20	-0.3	0.3

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline includes only those subjects with both a baseline value and a value for then summarized time period.

Cross Reference: Listing 16.2.9

Table 14.3.4.5 Summary of Vital Signs
Temperature (C)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Day 11-8hr Post	3	36.87	0.306	36.80	36.6	37.2	3	0.00	0.200	0.00	-0.2	0.2
	Day 11-12hr Post	3	36.83	0.321	36.70	36.6	37.2	3	-0.03	0.252	0.00	-0.3	0.2
	Day 11-16hr Post	3	36.77	0.153	36.80	36.6	36.9	3	-0.10	0.300	-0.10	-0.4	0.2
	Day 11-20hr Post	3	36.83	0.493	36.60	36.5	37.4	3	-0.03	0.723	-0.40	-0.5	0.8
	Day 14	3	36.60	0.100	36.60	36.5	36.7	3	-0.27	0.252	-0.30	-0.5	0.0
	Day 14-Pre-dose	3	36.57	0.058	36.60	36.5	36.6	3	-0.30	0.265	-0.40	-0.5	0.0
	Day 14-15min Post	3	36.93	0.321	36.80	36.7	37.3	3	0.07	0.551	-0.20	-0.3	0.7
	Day 14-1hr Post	3	36.70	0.200	36.70	36.5	36.9	3	-0.17	0.416	-0.30	-0.5	0.3
	Day 14-4hr Post	3	36.73	0.252	36.70	36.5	37.0	3	-0.13	0.153	-0.10	-0.3	0.0
	Day 14-8hr Post	3	36.63	0.231	36.50	36.5	36.9	3	-0.23	0.231	-0.10	-0.5	-0.1
	Day 14-12hr Post	3	36.90	0.300	36.90	36.6	37.2	3	0.03	0.153	0.00	-0.1	0.2
	Day 14-16hr Post	3	36.83	0.208	36.90	36.6	37.0	3	-0.03	0.351	0.00	-0.4	0.3
	Day 14-20hr Post	3	36.43	0.115	36.50	36.3	36.5	3	-0.43	0.306	-0.50	-0.7	-0.1
	Day 15	3	36.83	0.289	37.00	36.5	37.0	3	-0.03	0.058	0.00	-0.1	0.0
	Day 21	3	36.73	0.321	36.60	36.5	37.1	3	-0.13	0.252	-0.10	-0.4	0.1
	Month 2	3	36.63	0.252	36.60	36.4	36.9	3	-0.23	0.321	-0.10	-0.6	0.0
	Month 4	3	36.60	0.458	36.50	36.2	37.1	3	-0.27	0.473	-0.10	-0.8	0.1
	Month 6	3	36.63	0.586	36.40	36.2	37.3	3	-0.23	0.473	-0.40	-0.6	0.3
Cohort 2	Baseline	5	36.74	0.152	36.70	36.6	36.9						
	Day 0	5	36.84	0.134	36.90	36.7	37.0	5	0.10	0.122	0.10	0.0	0.3
	Day 0-Pre-dose	5	36.84	0.134	36.90	36.7	37.0	5	0.10	0.122	0.10	0.0	0.3
	Day 0-15min Post	5	36.90	0.418	37.00	36.2	37.3	5	0.16	0.522	0.20	-0.7	0.7
	Day 0-1hr Post	5	36.94	0.378	37.00	36.5	37.5	5	0.20	0.515	0.30	-0.4	0.9
	Day 0-4hr Post	5	36.92	0.327	36.80	36.6	37.4	5	0.18	0.455	0.00	-0.3	0.8
	Day 0-8hr Post	5	36.96	0.513	36.70	36.4	37.6	5	0.22	0.563	0.10	-0.5	1.0
	Day 0-12hr Post	5	36.92	0.572	36.70	36.2	37.6	5	0.18	0.630	0.10	-0.7	1.0
	Day 0-16hr Post	5	36.88	0.311	36.80	36.6	37.4	5	0.14	0.397	0.00	-0.2	0.8
	Day 0-20hr Post	5	36.88	0.342	36.80	36.4	37.3	5	0.14	0.351	0.10	-0.2	0.7
	Day 1	5	36.94	0.251	36.80	36.7	37.3	5	0.20	0.324	0.20	-0.2	0.7
	Day 4	5	36.84	0.241	36.90	36.5	37.1	5	0.10	0.224	0.10	-0.2	0.4
	Day 4-Pre-dose	5	36.68	0.249	36.50	36.5	37.0	5	-0.06	0.297	-0.10	-0.4	0.4
	Day 4-15min Post	5	36.88	0.217	37.00	36.6	37.1	5	0.14	0.321	0.10	-0.3	0.5
	Day 4-1hr Post	5	36.90	0.235	37.00	36.6	37.1	5	0.16	0.344	0.10	-0.3	0.5

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Cross Reference: Listing 16.2.9

Table 14.3.4.5 Summary of Vital Signs
Temperature (C)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 2	Day 4-4hr Post	5	37.00	0.406	37.00	36.5	37.6	5	0.26	0.428	0.10	-0.1	1.0
	Day 4-8hr Post	5	36.84	0.270	36.90	36.4	37.1	5	0.10	0.374	0.20	-0.5	0.4
	Day 4-12hr Post	5	36.88	0.268	37.00	36.6	37.2	5	0.14	0.321	0.30	-0.3	0.4
	Day 4-16hr Post	4	37.05	0.265	37.10	36.7	37.3	4	0.35	0.387	0.45	-0.2	0.7
	Day 4-20hr Post	4	37.00	0.245	37.05	36.7	37.2	4	0.30	0.216	0.25	0.1	0.6
	Day 7	5	36.92	0.192	36.90	36.7	37.2	5	0.18	0.239	0.30	-0.2	0.4
	Day 7-Pre-dose	5	36.90	0.200	36.80	36.7	37.2	5	0.16	0.230	0.20	-0.2	0.4
	Day 7-15min Post	5	36.94	0.230	36.90	36.7	37.3	5	0.20	0.235	0.30	-0.1	0.4
	Day 7-1hr Post	5	36.78	0.268	36.90	36.4	37.0	5	0.04	0.336	0.10	-0.5	0.4
	Day 7-4hr Post	5	36.86	0.279	36.80	36.6	37.2	5	0.12	0.277	0.20	-0.3	0.4
	Day 7-8hr Post	5	36.56	0.167	36.60	36.3	36.7	5	-0.18	0.249	-0.10	-0.6	0.0
	Day 7-12hr Post	5	36.80	0.495	37.00	36.0	37.3	5	0.06	0.627	0.30	-0.9	0.7
	Day 7-16hr Post	5	36.90	0.374	37.00	36.3	37.2	5	0.16	0.503	0.40	-0.6	0.6
	Day 7-20hr Post	5	36.68	0.228	36.70	36.4	36.9	5	-0.06	0.219	-0.20	-0.2	0.3
	Day 11	5	36.86	0.329	36.80	36.5	37.2	5	0.12	0.349	0.10	-0.3	0.6
	Day 11-Pre-dose	5	36.86	0.329	36.80	36.5	37.2	5	0.12	0.349	0.10	-0.3	0.6
	Day 11-15min Post	5	36.92	0.259	36.90	36.6	37.3	5	0.18	0.228	0.20	-0.1	0.4
	Day 11-1hr Post	5	36.92	0.370	36.90	36.6	37.5	5	0.18	0.303	0.00	-0.1	0.6
	Day 11-4hr Post	5	36.62	0.567	36.40	36.2	37.6	5	-0.12	0.526	-0.20	-0.7	0.7
	Day 11-8hr Post	5	36.74	0.416	36.70	36.3	37.3	5	0.00	0.430	0.10	-0.5	0.4
	Day 11-12hr Post	5	36.60	0.367	36.80	36.2	36.9	5	-0.14	0.456	-0.10	-0.7	0.3
	Day 11-16hr Post	5	36.66	0.336	36.90	36.2	36.9	5	-0.08	0.396	0.00	-0.7	0.3
	Day 11-20hr Post	5	36.86	0.230	36.80	36.6	37.1	5	0.12	0.295	0.20	-0.3	0.5
	Day 14	5	37.16	0.270	37.10	36.9	37.6	5	0.42	0.228	0.40	0.2	0.7
	Day 14-Pre-dose	5	37.16	0.270	37.10	36.9	37.6	5	0.42	0.228	0.40	0.2	0.7
	Day 14-15min Post	5	36.76	0.550	37.00	35.8	37.1	5	0.02	0.646	0.20	-1.1	0.5
	Day 14-1hr Post	5	37.02	0.517	37.10	36.5	37.8	5	0.28	0.606	0.20	-0.3	1.2
	Day 14-4hr Post	5	36.76	0.297	36.90	36.4	37.1	5	0.02	0.327	0.20	-0.5	0.3
	Day 14-8hr Post	5	36.76	0.261	36.80	36.4	37.0	5	0.02	0.409	0.10	-0.5	0.4
	Day 14-12hr Post	5	36.92	0.432	36.90	36.4	37.6	5	0.18	0.438	0.30	-0.5	0.7
	Day 14-16hr Post	5	36.96	0.270	37.00	36.5	37.2	5	0.22	0.377	0.30	-0.4	0.6
	Day 14-20hr Post	5	36.82	0.319	36.90	36.4	37.2	5	0.08	0.460	0.30	-0.5	0.6
	Day 15	5	36.96	0.270	37.00	36.5	37.2	5	0.22	0.377	0.30	-0.4	0.6
	Day 21	5	36.86	0.114	36.90	36.7	37.0	5	0.12	0.205	0.10	-0.2	0.3

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Cross Reference: Listing 16.2.9

Table 14.3.4.5 Summary of Vital Signs
Temperature (C)

		Actual Values						Change From Baseline				
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 2	Month 2	5	37.14	0.219	37.20	36.8	37.4	5	0.40	0.332	0.50	-0.1	0.8
	Month 4	4	37.23	0.386	37.05	37.0	37.8	4	0.52	0.250	0.40	0.4	0.9
	Month 6	5	36.98	0.492	37.20	36.4	37.4	5	0.24	0.445	0.30	-0.3	0.8
Cohort 3	Baseline	2	36.10	0.141	36.10	36.0	36.2						
	Day 0	2	36.90	0.000	36.90	36.9	36.9	2	0.80	0.141	0.80	0.7	0.9
	Day 0-Pre-dose	2	36.90	0.000	36.90	36.9	36.9	2	0.80	0.141	0.80	0.7	0.9
	Day 0-15min Post	2	36.90	0.000	36.90	36.9	36.9	2	0.80	0.141	0.80	0.7	0.9
	Day 0-1hr Post	2	36.45	0.071	36.45	36.4	36.5	2	0.35	0.212	0.35	0.2	0.5
	Day 0-4hr Post	2	36.50	0.141	36.50	36.4	36.6	2	0.40	0.000	0.40	0.4	0.4
	Day 0-8hr Post	1	36.60		36.60	36.6	36.6	1	0.40		0.40	0.4	0.4
	Day 0-12hr Post	2	36.85	0.071	36.85	36.8	36.9	2	0.75	0.212	0.75	0.6	0.9
	Day 0-16hr Post	2	36.90	0.283	36.90	36.7	37.1	2	0.80	0.424	0.80	0.5	1.1
	Day 0-20hr Post	2	36.70	0.283	36.70	36.5	36.9	2	0.60	0.141	0.60	0.5	0.7
	Day 0-24hr Post	2	36.65	0.354	36.65	36.4	36.9	2	0.55	0.212	0.55	0.4	0.7
	Day 1	2	36.65	0.354	36.65	36.4	36.9	2	0.55	0.212	0.55	0.4	0.7
	Day 4	2	36.55	0.071	36.55	36.5	36.6	2	0.45	0.071	0.45	0.4	0.5
	Day 4-Pre-dose	2	36.55	0.071	36.55	36.5	36.6	2	0.45	0.071	0.45	0.4	0.5
	Day 4-15min Post	2	36.70	0.424	36.70	36.4	37.0	2	0.60	0.283	0.60	0.4	0.8
	Day 4-1hr Post	2	36.60	0.000	36.60	36.6	36.6	2	0.50	0.141	0.50	0.4	0.6
	Day 4-4hr Post	2	36.90	0.283	36.90	36.7	37.1	2	0.80	0.424	0.80	0.5	1.1
	Day 4-8hr Post	2	36.75	0.212	36.75	36.6	36.9	2	0.65	0.071	0.65	0.6	0.7
	Day 4-12hr Post	2	37.10	1.131	37.10	36.3	37.9	2	1.00	0.990	1.00	0.3	1.7
	Day 4-16hr Post	2	36.70	0.141	36.70	36.6	36.8	2	0.60	0.283	0.60	0.4	0.8
	Day 4-20hr Post	2	36.85	0.212	36.85	36.7	37.0	2	0.75	0.071	0.75	0.7	0.8
	Day 4-24hr Post	2	36.50	0.000	36.50	36.5	36.5	2	0.40	0.141	0.40	0.3	0.5
	Day 7	2	36.45	0.636	36.45	36.0	36.9	2	0.35	0.495	0.35	0.0	0.7
	Day 7-Pre-dose	2	36.45	0.636	36.45	36.0	36.9	2	0.35	0.495	0.35	0.0	0.7
	Day 7-15min Post	2	36.65	0.212	36.65	36.5	36.8	2	0.55	0.354	0.55	0.3	0.8
	Day 7-1hr Post	2	36.05	0.071	36.05	36.0	36.1	2	-0.05	0.071	-0.05	-0.1	0.0
	Day 7-4hr Post	2	36.55	0.212	36.55	36.4	36.7	2	0.45	0.071	0.45	0.4	0.5
	Day 7-8hr Post	2	36.45	0.636	36.45	36.0	36.9	2	0.35	0.495	0.35	0.0	0.7
	Day 7-12hr Post	2	36.65	0.636	36.65	36.2	37.1	2	0.55	0.495	0.55	0.2	0.9
	Day 7-16hr Post	2	36.85	0.495	36.85	36.5	37.2	2	0.75	0.636	0.75	0.3	1.2

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline includes only those subjects with both a baseline value and a value for then summarized time period.

Cross Reference: Listing 16.2.9

Table 14.3.4.5 Summary of Vital Signs
Temperature (C)

		Actual Values						Change From Baseline				
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 3	Day 7-20hr Post	2	36.80	0.283	36.80	36.6	37.0	2	0.70	0.424	0.70	0.4	1.0
	Day 7-24hr Post	2	36.60	0.283	36.60	36.4	36.8	2	0.50	0.424	0.50	0.2	0.8
	Day 11	2	37.05	0.636	37.05	36.6	37.5	2	0.95	0.495	0.95	0.6	1.3
	Day 11-Pre-dose	2	37.05	0.636	37.05	36.6	37.5	2	0.95	0.495	0.95	0.6	1.3
	Day 11-15min Post	2	36.50	0.141	36.50	36.4	36.6	2	0.40	0.283	0.40	0.2	0.6
	Day 11-1hr Post	2	36.75	0.495	36.75	36.4	37.1	2	0.65	0.354	0.65	0.4	0.9
	Day 11-4hr Post	2	36.50	0.141	36.50	36.4	36.6	2	0.40	0.000	0.40	0.4	0.4
	Day 11-8hr Post	2	36.85	0.212	36.85	36.7	37.0	2	0.75	0.071	0.75	0.7	0.8
	Day 11-12hr Post	2	36.85	0.212	36.85	36.7	37.0	2	0.75	0.071	0.75	0.7	0.8
	Day 11-16hr Post	2	36.95	0.354	36.95	36.7	37.2	2	0.85	0.495	0.85	0.5	1.2
	Day 11-20hr Post	2	36.45	0.071	36.45	36.4	36.5	2	0.35	0.071	0.35	0.3	0.4
	Day 11-24hr Post	2	36.60	0.424	36.60	36.3	36.9	2	0.50	0.283	0.50	0.3	0.7
	Day 14	2	36.70	0.141	36.70	36.6	36.8	2	0.60	0.283	0.60	0.4	0.8
	Day 14-Pre-dose	2	36.70	0.141	36.70	36.6	36.8	2	0.60	0.283	0.60	0.4	0.8
	Day 14-15min Post	2	36.80	1.131	36.80	36.0	37.6	2	0.70	0.990	0.70	0.0	1.4
	Day 14-1hr Post	2	36.40	0.566	36.40	36.0	36.8	2	0.30	0.424	0.30	0.0	0.6
	Day 14-4hr Post	2	36.40	0.424	36.40	36.1	36.7	2	0.30	0.566	0.30	-0.1	0.7
	Day 14-8hr Post	2	36.90	0.283	36.90	36.7	37.1	2	0.80	0.424	0.80	0.5	1.1
	Day 14-12hr Post	2	36.85	0.071	36.85	36.8	36.9	2	0.75	0.071	0.75	0.7	0.8
	Day 14-16hr Post	2	36.60	0.566	36.60	36.2	37.0	2	0.50	0.424	0.50	0.2	0.8
	Day 14-20hr Post	2	36.65	0.495	36.65	36.3	37.0	2	0.55	0.354	0.55	0.3	0.8
	Day 14-24hr Post	2	36.30	0.141	36.30	36.2	36.4	2	0.20	0.000	0.20	0.2	0.2
	Day 15	2	36.50	0.707	36.50	36.0	37.0	2	0.40	0.566	0.40	0.0	0.8
	Day 21	2	36.40	0.566	36.40	36.0	36.8	2	0.30	0.424	0.30	0.0	0.6
	Month 2	2	36.15	0.354	36.15	35.9	36.4	2	0.05	0.495	0.05	-0.3	0.4
	Month 4	2	36.50	0.283	36.50	36.3	36.7	2	0.40	0.424	0.40	0.1	0.7
	Month 6	2	36.25	0.071	36.25	36.2	36.3	2	0.15	0.212	0.15	0.0	0.3
Overall	Baseline	10	36.65	0.334	36.65	36.0	37.0						
	Day 0	10	36.81	0.173	36.90	36.4	37.0	10	0.16	0.427	0.10	-0.6	0.9
	Day 0-Pre-dose	10	36.82	0.175	36.90	36.4	37.0	10	0.17	0.419	0.10	-0.6	0.9
	Day 0-15min Post	10	36.89	0.296	36.90	36.2	37.3	10	0.24	0.481	0.20	-0.7	0.9
	Day 0-1hr Post	10	36.77	0.416	36.75	36.1	37.5	10	0.12	0.539	0.25	-0.9	0.9
	Day 0-4hr Post	10	36.74	0.299	36.65	36.4	37.4	10	0.09	0.428	0.05	-0.5	0.8

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Cross Reference: Listing 16.2.9

Table 14.3.4.5 Summary of Vital Signs
Temperature (C)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Overall	Day 0-8hr Post	9	36.97	0.512	36.70	36.4	37.8	9	0.24	0.594	0.10	-0.5	1.2
	Day 0-12hr Post	10	36.86	0.433	36.75	36.2	37.6	10	0.21	0.605	0.30	-0.7	1.0
	Day 0-16hr Post	10	36.88	0.329	36.80	36.4	37.4	10	0.23	0.548	0.10	-0.6	1.1
	Day 0-20hr Post	10	36.84	0.284	36.85	36.4	37.3	10	0.19	0.370	0.15	-0.4	0.7
	Day 0-24hr Post	2	36.65	0.354	36.65	36.4	36.9	2	0.55	0.212	0.55	0.4	0.7
	Day 1	10	36.88	0.249	36.85	36.4	37.3	10	0.23	0.313	0.20	-0.2	0.7
	Day 4	10	36.73	0.226	36.65	36.5	37.1	10	0.08	0.349	0.15	-0.5	0.5
	Day 4-Pre-dose	10	36.65	0.201	36.55	36.5	37.0	10	0.00	0.377	-0.05	-0.5	0.5
	Day 4-15min Post	10	36.86	0.250	36.95	36.4	37.2	10	0.21	0.384	0.25	-0.3	0.8
	Day 4-1hr Post	10	36.79	0.242	36.80	36.4	37.1	10	0.14	0.392	0.20	-0.6	0.6
	Day 4-4hr Post	10	37.01	0.443	36.90	36.5	37.9	10	0.36	0.589	0.15	-0.4	1.3
	Day 4-8hr Post	10	36.81	0.202	36.85	36.4	37.1	10	0.16	0.375	0.15	-0.5	0.7
	Day 4-12hr Post	10	36.93	0.430	36.95	36.3	37.9	10	0.28	0.561	0.30	-0.3	1.7
	Day 4-16hr Post	9	36.84	0.288	36.80	36.4	37.3	9	0.22	0.458	0.40	-0.6	0.8
	Day 4-20hr Post	9	36.90	0.218	36.90	36.6	37.2	9	0.28	0.349	0.20	-0.2	0.8
	Day 4-24hr Post	2	36.50	0.000	36.50	36.5	36.5	2	0.40	0.141	0.40	0.3	0.5
	Day 7	10	36.84	0.327	36.90	36.0	37.2	10	0.19	0.264	0.20	-0.2	0.7
	Day 7-Pre-dose	10	36.81	0.314	36.90	36.0	37.2	10	0.16	0.276	0.15	-0.2	0.7
	Day 7-15min Post	10	36.83	0.298	36.80	36.3	37.3	10	0.18	0.437	0.30	-0.7	0.8
	Day 7-1hr Post	10	36.67	0.422	36.75	36.0	37.3	10	0.02	0.316	0.05	-0.5	0.4
	Day 7-4hr Post	10	36.73	0.283	36.70	36.3	37.2	10	0.08	0.371	0.15	-0.7	0.5
	Day 7-8hr Post	10	36.65	0.366	36.65	36.0	37.3	10	0.00	0.427	0.00	-0.6	0.7
	Day 7-12hr Post	10	36.71	0.423	36.80	36.0	37.3	10	0.06	0.587	0.25	-0.9	0.9
	Day 7-16hr Post	10	36.91	0.370	37.00	36.3	37.4	10	0.26	0.566	0.35	-0.6	1.2
	Day 7-20hr Post	10	36.74	0.207	36.80	36.4	37.0	10	0.09	0.381	-0.05	-0.2	1.0
	Day 7-24hr Post	2	36.60	0.283	36.60	36.4	36.8	2	0.50	0.424	0.50	0.2	0.8
	Day 11	10	36.84	0.401	36.70	36.4	37.5	10	0.19	0.608	0.20	-0.6	1.3
	Day 11-Pre-dose	10	36.84	0.401	36.70	36.4	37.5	10	0.19	0.608	0.20	-0.6	1.3
	Day 11-15min Post	10	36.78	0.257	36.75	36.4	37.3	10	0.13	0.323	0.20	-0.4	0.6
	Day 11-1hr Post	10	36.81	0.341	36.80	36.4	37.5	10	0.16	0.445	0.15	-0.6	0.9
	Day 11-4hr Post	10	36.65	0.401	36.60	36.2	37.6	10	0.00	0.437	-0.10	-0.7	0.7
	Day 11-8hr Post	10	36.80	0.327	36.75	36.3	37.3	10	0.15	0.438	0.15	-0.5	0.8
	Day 11-12hr Post	10	36.72	0.322	36.75	36.2	37.2	10	0.07	0.488	0.10	-0.7	0.8
	Day 11-16hr Post	10	36.75	0.288	36.85	36.2	37.2	10	0.10	0.523	0.10	-0.7	1.2

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Baseline value is the last value taken prior to study drug administration.
Change from baseline includes only those subjects with both a baseline value and a value for then summarized time period.

Cross Reference: Listing 16.2.9

Table 14.3.4.5 Summary of Vital Signs
Temperature (C)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Overall	Day 11-20hr Post	10	36.77	0.327	36.65	36.4	37.4	10	0.12	0.418	0.20	-0.5	0.8
	Day 11-24hr Post	2	36.60	0.424	36.60	36.3	36.9	2	0.50	0.283	0.50	0.3	0.7
	Day 14	10	36.90	0.337	36.85	36.5	37.6	10	0.25	0.422	0.30	-0.5	0.8
	Day 14-Pre-dose	10	36.89	0.345	36.85	36.5	37.6	10	0.24	0.438	0.30	-0.5	0.8
	Day 14-15min Post	10	36.82	0.553	36.90	35.8	37.6	10	0.17	0.663	0.15	-1.1	1.4
	Day 14-1hr Post	10	36.80	0.478	36.75	36.0	37.8	10	0.15	0.519	0.10	-0.5	1.2
	Day 14-4hr Post	10	36.68	0.308	36.70	36.1	37.1	10	0.03	0.337	-0.05	-0.5	0.7
	Day 14-8hr Post	10	36.75	0.246	36.75	36.4	37.1	10	0.10	0.506	-0.00	-0.5	1.1
	Day 14-12hr Post	10	36.90	0.323	36.90	36.4	37.6	10	0.25	0.406	0.25	-0.5	0.8
	Day 14-16hr Post	10	36.85	0.314	37.00	36.2	37.2	10	0.20	0.386	0.25	-0.4	0.8
	Day 14-20hr Post	10	36.67	0.327	36.55	36.3	37.2	10	0.02	0.512	0.10	-0.7	0.8
	Day 14-24hr Post	2	36.30	0.141	36.30	36.2	36.4	2	0.20	0.000	0.20	0.2	0.2
	Day 15	10	36.83	0.374	37.00	36.0	37.2	10	0.18	0.355	0.10	-0.4	0.8
	Day 21	10	36.73	0.313	36.80	36.0	37.1	10	0.08	0.282	0.10	-0.4	0.6
	Month 2	10	36.79	0.465	36.85	35.9	37.4	10	0.14	0.430	0.15	-0.6	0.8
	Month 4	9	36.86	0.493	37.00	36.2	37.8	9	0.23	0.495	0.40	-0.8	0.9
	Month 6	10	36.73	0.523	36.45	36.2	37.4	10	0.08	0.437	0.15	-0.6	0.8
Siblings	Enrollment	4	36.83	0.512	36.80	36.3	37.4						

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Cross Reference: Listing 16.2.9

Table 14.3.4.5 Summary of Vital Signs

Systolic Blood Pressure (mmHg)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Baseline	3	81.3	14.57	86.0	65	93						
	Day 0	3	96.3	16.74	106.0	77	106	3	15.0	4.36	13.0	12	20
	Day 0-Pre-dose	3	94.7	19.63	106.0	72	106	3	13.3	6.51	13.0	7	20
	Day 0-15min Post	3	87.3	20.79	79.0	72	111	3	6.0	12.53	7.0	-7	18
	Day 0-1hr Post	3	84.0	10.00	84.0	74	94	3	2.7	5.69	1.0	-2	9
	Day 0-4hr Post	3	75.0	23.64	72.0	53	100	3	-6.3	11.59	-12.0	-14	7
	Day 0-8hr Post	3	87.3	5.51	90.0	81	91	3	6.0	9.54	5.0	-3	16
	Day 0-12hr Post	3	89.3	8.50	89.0	81	98	3	8.0	10.58	12.0	-4	16
	Day 0-16hr Post	3	76.7	15.14	70.0	66	94	3	-4.7	16.26	1.0	-23	8
	Day 0-20hr Post	3	86.7	12.22	84.0	76	100	3	5.3	6.66	7.0	-2	11
	Day 1	3	83.3	17.01	84.0	66	100	3	2.0	4.58	1.0	-2	7
	Day 4	3	88.3	14.19	91.0	73	101	3	7.0	1.73	8.0	5	8
	Day 4-Pre-dose	3	88.3	14.19	91.0	73	101	3	7.0	1.73	8.0	5	8
	Day 4-15min Post	3	92.7	16.26	96.0	75	107	3	11.3	2.31	10.0	10	14
	Day 4-1hr Post	3	89.0	8.54	90.0	80	97	3	7.7	6.35	4.0	4	15
	Day 4-4hr Post	3	91.0	5.57	90.0	86	97	3	9.7	9.81	4.0	4	21
	Day 4-8hr Post	2	85.0	11.31	85.0	77	93	2	9.5	3.54	9.5	7	12
	Day 4-12hr Post	3	87.3	13.01	88.0	74	100	3	6.0	3.61	7.0	2	9
	Day 4-16hr Post	3	101.7	6.43	99.0	97	109	3	20.3	13.20	23.0	6	32
	Day 4-20hr Post	3	89.7	8.74	92.0	80	97	3	8.3	5.86	6.0	4	15
	Day 7	3	83.0	13.45	87.0	68	94	3	1.7	1.15	1.0	1	3
	Day 7-Pre-dose	3	80.0	18.52	87.0	59	94	3	-1.3	4.04	1.0	-6	1
	Day 7-15min Post	3	82.3	16.01	83.0	66	98	3	1.0	11.00	1.0	-10	12
	Day 7-1hr Post	3	87.0	6.08	90.0	80	91	3	5.7	9.02	5.0	-3	15
	Day 7-4hr Post	3	104.3	18.90	111.0	83	119	3	23.0	8.66	18.0	18	33
	Day 7-8hr Post	3	78.3	15.04	77.0	64	94	3	-3.0	12.12	-1.0	-16	8
	Day 7-12hr Post	3	79.0	9.64	83.0	68	86	3	-2.3	5.03	-3.0	-7	3
	Day 7-16hr Post	3	87.7	15.50	88.0	72	103	3	6.3	23.86	17.0	-21	23
	Day 7-20hr Post	3	88.0	13.23	83.0	78	103	3	6.7	18.77	17.0	-15	18
	Day 11	3	88.0	19.08	98.0	66	100	3	6.7	6.66	5.0	1	14
	Day 11-Pre-dose	3	88.0	19.08	98.0	66	100	3	6.7	6.66	5.0	1	14
	Day 11-15min Post	3	90.7	14.29	94.0	75	103	3	9.3	8.02	10.0	1	17
	Day 11-1hr Post	3	82.0	5.00	82.0	77	87	3	0.7	14.22	-6.0	-9	17
	Day 11-4hr Post	3	95.0	30.12	88.0	69	128	3	13.7	27.23	23.0	-17	35

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Cross Reference: Listing 16.2.9

Table 14.3.4.5 Summary of Vital Signs
Systolic Blood Pressure (mmHg)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Day 11-8hr Post	3	105.0	28.69	119.0	72	124	3	23.7	15.63	26.0	7	38
	Day 11-12hr Post	3	78.0	13.11	76.0	66	92	3	-3.3	5.86	-1.0	-10	1
	Day 11-16hr Post	3	85.7	11.02	91.0	73	93	3	4.3	4.04	5.0	0	8
	Day 11-20hr Post	3	86.7	6.81	89.0	79	92	3	5.3	9.02	6.0	-4	14
	Day 14	3	92.3	17.79	96.0	73	108	3	11.0	9.85	8.0	3	22
	Day 14-Pre-dose	3	94.3	14.57	96.0	79	108	3	13.0	9.54	14.0	3	22
	Day 14-15min Post	3	89.7	13.61	85.0	79	105	3	8.3	19.35	19.0	-14	20
	Day 14-1hr Post	3	91.0	1.00	91.0	90	92	3	9.7	15.53	5.0	-3	27
	Day 14-4hr Post	3	90.0	5.29	88.0	86	96	3	8.7	13.05	10.0	-5	21
	Day 14-8hr Post	3	92.7	15.18	90.0	79	109	3	11.3	21.96	23.0	-14	25
	Day 14-12hr Post	3	98.0	22.91	93.0	78	123	3	16.7	18.77	13.0	0	37
	Day 14-16hr Post	3	84.7	2.08	84.0	83	87	3	3.3	13.65	-3.0	-6	19
	Day 14-20hr Post	3	83.0	5.29	81.0	79	89	3	1.7	13.05	3.0	-12	14
	Day 15	3	85.0	4.58	84.0	81	90	3	3.7	15.50	4.0	-12	19
	Day 21	3	78.3	9.29	81.0	68	86	3	-3.0	5.29	-5.0	-7	3
	Month 2	3	85.0	5.00	85.0	80	90	3	3.7	9.87	-1.0	-3	15
	Month 4	3	93.3	9.45	90.0	86	104	3	12.0	8.54	11.0	4	21
	Month 6	3	101.0	16.09	103.0	84	116	3	19.7	10.02	19.0	10	30
Cohort 2	Baseline	5	77.2	8.23	80.0	64	85						
	Day 0	5	75.6	15.63	84.0	49	86	5	-1.6	9.91	0.0	-15	9
	Day 0-Pre-dose	5	75.6	15.63	84.0	49	86	5	-1.6	9.91	0.0	-15	9
	Day 0-15min Post	5	80.6	14.15	81.0	65	97	5	3.4	12.97	1.0	-14	22
	Day 0-1hr Post	5	85.8	23.85	86.0	51	117	5	8.6	17.47	6.0	-13	32
	Day 0-4hr Post	5	83.0	22.01	70.0	65	115	5	5.8	20.13	4.0	-17	30
	Day 0-8hr Post	5	81.4	13.65	80.0	67	101	5	4.2	12.36	7.0	-15	16
	Day 0-12hr Post	5	68.4	11.67	74.0	51	79	5	-8.8	9.15	-11.0	-20	4
	Day 0-16hr Post	5	80.6	17.40	90.0	52	93	5	3.4	12.40	5.0	-12	18
	Day 0-20hr Post	5	80.8	11.19	83.0	69	95	5	3.6	11.80	5.0	-12	20
	Day 1	5	80.6	12.46	83.0	62	95	5	3.4	10.43	-2.0	-6	20
	Day 4	5	80.8	16.08	78.0	62	106	5	3.6	11.15	-2.0	-7	21
	Day 4-Pre-dose	5	80.8	16.08	78.0	62	106	5	3.6	11.15	-2.0	-7	21
	Day 4-15min Post	5	78.4	10.88	80.0	60	87	5	1.2	5.89	-1.0	-4	11
	Day 4-1hr Post	5	87.6	14.33	88.0	66	101	5	10.4	7.44	13.0	2	18

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline includes only those subjects with both a baseline value and a value for then summarized time period.

Cross Reference: Listing 16.2.9

Table 14.3.4.5 Summary of Vital Signs
Systolic Blood Pressure (mmHg)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 2	Day 4-4hr Post	5	77.8	18.65	85.0	54	99	5	0.6	14.57	5.0	-19	14
	Day 4-8hr Post	5	79.2	11.71	85.0	63	91	5	2.0	9.27	0.0	-11	11
	Day 4-12hr Post	5	79.2	13.20	81.0	60	93	5	2.0	10.22	1.0	-9	18
	Day 4-16hr Post	4	69.5	3.70	69.5	65	74	4	-8.3	7.41	-9.0	-16	1
	Day 4-20hr Post	4	70.0	11.75	71.0	56	82	4	-7.8	12.31	-3.0	-26	1
	Day 7	5	76.6	10.71	76.0	66	94	5	-0.6	13.52	-4.0	-16	19
	Day 7-Pre-dose	5	76.6	10.71	76.0	66	94	5	-0.6	13.52	-4.0	-16	19
	Day 7-15min Post	5	77.0	16.57	84.0	57	95	5	-0.2	14.91	4.0	-25	12
	Day 7-1hr Post	5	81.6	21.34	84.0	59	114	5	4.4	16.89	4.0	-16	29
	Day 7-4hr Post	5	89.4	16.68	83.0	71	112	5	12.2	15.27	19.0	-11	27
	Day 7-8hr Post	5	69.2	10.78	66.0	55	81	5	-8.0	12.19	-4.0	-25	4
	Day 7-12hr Post	5	85.4	9.50	89.0	69	93	5	8.2	3.42	10.0	4	11
	Day 7-16hr Post	5	80.2	7.05	82.0	73	89	5	3.0	8.92	2.0	-9	14
	Day 7-20hr Post	5	73.6	10.26	74.0	62	89	5	-3.6	12.82	-6.0	-20	14
	Day 11	5	84.2	16.02	90.0	67	105	5	7.0	11.98	8.0	-11	20
	Day 11-Pre-dose	5	85.6	16.94	90.0	67	105	5	8.4	13.46	8.0	-11	22
	Day 11-15min Post	5	79.0	16.48	69.0	66	102	5	1.8	15.61	5.0	-15	17
	Day 11-1hr Post	5	79.0	17.61	71.0	63	107	5	1.8	14.31	-1.0	-13	22
	Day 11-4hr Post	5	84.4	10.69	82.0	70	95	5	7.2	13.31	10.0	-12	20
	Day 11-8hr Post	5	75.6	16.04	70.0	58	94	5	-1.6	14.22	-6.0	-17	19
	Day 11-12hr Post	5	77.2	11.03	78.0	62	89	5	0.0	14.78	1.0	-20	14
	Day 11-16hr Post	5	78.4	19.40	68.0	62	105	5	1.2	19.37	0.0	-20	30
	Day 11-20hr Post	5	78.4	8.02	81.0	65	86	5	1.2	1.10	1.0	0	3
	Day 14	5	84.6	4.77	86.0	77	90	5	7.4	6.35	6.0	1	15
	Day 14-Pre-dose	4	84.3	5.44	85.0	77	90	4	9.0	6.06	9.5	2	15
	Day 14-15min Post	4	76.8	9.03	76.0	69	86	4	1.5	9.29	3.0	-11	11
	Day 14-1hr Post	4	79.8	7.80	82.0	69	86	4	4.5	4.51	4.5	-1	10
	Day 14-4hr Post	5	80.4	11.15	78.0	68	97	5	3.2	11.65	3.0	-7	22
	Day 14-8hr Post	5	76.2	7.26	72.0	69	85	5	-1.0	5.15	-2.0	-8	5
	Day 14-12hr Post	5	84.2	9.52	87.0	71	94	5	7.0	13.44	3.0	-9	27
	Day 14-16hr Post	5	85.4	10.45	81.0	76	101	5	8.2	9.18	12.0	-4	16
	Day 14-20hr Post	5	81.0	8.51	85.0	68	89	5	3.8	6.53	4.0	-5	11
	Day 15	4	81.5	6.66	79.5	76	91	4	6.3	9.32	6.5	-4	16
	Day 21	5	84.2	11.95	78.0	75	102	5	7.0	11.94	14.0	-7	17

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline includes only those subjects with both a baseline value and a value for then summarized time period.

Cross Reference: Listing 16.2.9

Table 14.3.4.5 Summary of Vital Signs
Systolic Blood Pressure (mmHg)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 2	Month 2	5	82.8	7.89	83.0	73	91	5	5.6	14.91	1.0	-8	26
	Month 4	5	102.0	7.31	105.0	92	110	5	24.8	13.70	26.0	10	41
	Month 6	5	101.6	13.24	103.0	82	114	5	24.4	13.41	29.0	7	39
Cohort 3	Baseline	2	90.5	10.61	90.5	83	98						
	Day 0	2	77.5	27.58	77.5	58	97	2	-13.0	16.97	-13.0	-25	-1
	Day 0-Pre-dose	2	78.0	26.87	78.0	59	97	2	-12.5	16.26	-12.5	-24	-1
	Day 0-15min Post	2	83.0	5.66	83.0	79	87	2	-7.5	4.95	-7.5	-11	-4
	Day 0-1hr Post	2	92.5	4.95	92.5	89	96	2	2.0	5.66	2.0	-2	6
	Day 0-4hr Post	2	87.0	9.90	87.0	80	94	2	-3.5	0.71	-3.5	-4	-3
	Day 0-8hr Post	1	91.0		91.0	91	91	1	-7.0		-7.0	-7	-7
	Day 0-12hr Post	2	75.0	8.49	75.0	69	81	2	-15.5	2.12	-15.5	-17	-14
	Day 0-16hr Post	2	86.5	3.54	86.5	84	89	2	-4.0	14.14	-4.0	-14	6
	Day 0-20hr Post	2	96.5	4.95	96.5	93	100	2	6.0	15.56	6.0	-5	17
	Day 0-24hr Post	1	98.0		98.0	98	98	1	0.0		0.0	0	0
	Day 1	2	82.5	14.85	82.5	72	93	2	-8.0	4.24	-8.0	-11	-5
	Day 4	2	86.5	30.41	86.5	65	108	2	-4.0	19.80	-4.0	-18	10
	Day 4-Pre-dose	2	86.5	30.41	86.5	65	108	2	-4.0	19.80	-4.0	-18	10
	Day 4-15min Post	2	84.0	5.66	84.0	80	88	2	-6.5	4.95	-6.5	-10	-3
	Day 4-1hr Post	2	98.0	14.14	98.0	88	108	2	7.5	3.54	7.5	5	10
	Day 4-4hr Post	2	82.5	0.71	82.5	82	83	2	-8.0	9.90	-8.0	-15	-1
	Day 4-8hr Post	2	85.0	11.31	85.0	77	93	2	-5.5	21.92	-5.5	-21	10
	Day 4-12hr Post	2	78.0	4.24	78.0	75	81	2	-12.5	14.85	-12.5	-23	-2
	Day 4-16hr Post	2	86.0	9.90	86.0	79	93	2	-4.5	0.71	-4.5	-5	-4
	Day 4-20hr Post	2	105.0	9.90	105.0	98	112	2	14.5	0.71	14.5	14	15
	Day 4-24hr Post	2	82.0	8.49	82.0	76	88	2	-8.5	2.12	-8.5	-10	-7
	Day 7	2	79.0	18.38	79.0	66	92	2	-11.5	7.78	-11.5	-17	-6
	Day 7-Pre-dose	2	79.0	18.38	79.0	66	92	2	-11.5	7.78	-11.5	-17	-6
	Day 7-15min Post	2	86.5	19.09	86.5	73	100	2	-4.0	8.49	-4.0	-10	2
	Day 7-1hr Post	2	92.5	16.26	92.5	81	104	2	2.0	26.87	2.0	-17	21
	Day 7-4hr Post	2	93.0	18.38	93.0	80	106	2	2.5	7.78	2.5	-3	8
	Day 7-8hr Post	2	81.0	28.28	81.0	61	101	2	-9.5	17.68	-9.5	-22	3
	Day 7-12hr Post	2	83.5	12.02	83.5	75	92	2	-7.0	1.41	-7.0	-8	-6
	Day 7-16hr Post	2	84.5	7.78	84.5	79	90	2	-6.0	2.83	-6.0	-8	-4

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline includes only those subjects with both a baseline value and a value for then summarized time period.

Cross Reference: Listing 16.2.9

Table 14.3.4.5 Summary of Vital Signs
Systolic Blood Pressure (mmHg)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 3	Day 7-20hr Post	2	93.5	6.36	93.5	89	98	2	3.0	4.24	3.0	0	6
	Day 7-24hr Post	2	86.0	26.87	86.0	67	105	2	-4.5	16.26	-4.5	-16	7
	Day 11	2	76.5	4.95	76.5	73	80	2	-14.0	5.66	-14.0	-18	-10
	Day 11-Pre-dose	2	76.5	4.95	76.5	73	80	2	-14.0	5.66	-14.0	-18	-10
	Day 11-15min Post	2	78.5	10.61	78.5	71	86	2	-12.0	0.00	-12.0	-12	-12
	Day 11-1hr Post	2	97.0	8.49	97.0	91	103	2	6.5	19.09	6.5	-7	20
	Day 11-4hr Post	2	106.0	7.07	106.0	101	111	2	15.5	3.54	15.5	13	18
	Day 11-8hr Post	2	97.5	6.36	97.5	93	102	2	7.0	4.24	7.0	4	10
	Day 11-12hr Post	1	94.0		94.0	94	94	1	-4.0		-4.0	-4	-4
	Day 11-16hr Post	1	78.0		78.0	78	78	1	-20.0		-20.0	-20	-20
	Day 11-20hr Post	2	100.0	11.31	100.0	92	108	2	9.5	0.71	9.5	9	10
	Day 11-24hr Post	2	94.0	7.07	94.0	89	99	2	3.5	3.54	3.5	1	6
	Day 14	2	107.5	10.61	107.5	100	115	2	17.0	0.00	17.0	17	17
	Day 14-Pre-dose	2	107.5	10.61	107.5	100	115	2	17.0	0.00	17.0	17	17
	Day 14-15min Post	2	88.5	10.61	88.5	81	96	2	-2.0	0.00	-2.0	-2	-2
	Day 14-1hr Post	2	104.5	14.85	104.5	94	115	2	14.0	25.46	14.0	-4	32
	Day 14-4hr Post	2	113.5	3.54	113.5	111	116	2	23.0	7.07	23.0	18	28
	Day 14-8hr Post	2	101.5	0.71	101.5	101	102	2	11.0	11.31	11.0	3	19
	Day 14-12hr Post	2	78.0	8.49	78.0	72	84	2	-12.5	19.09	-12.5	-26	1
	Day 14-16hr Post	2	100.5	37.48	100.5	74	127	2	10.0	48.08	10.0	-24	44
	Day 14-20hr Post	2	88.0	4.24	88.0	85	91	2	-2.5	6.36	-2.5	-7	2
	Day 14-24hr Post	1	79.0		79.0	79	79	1	-19.0		-19.0	-19	-19
	Day 15	2	79.0	7.07	79.0	74	84	2	-11.5	17.68	-11.5	-24	1
	Day 21	2	82.5	9.19	82.5	76	89	2	-8.0	1.41	-8.0	-9	-7
	Month 2	2	78.5	28.99	78.5	58	99	2	-12.0	18.38	-12.0	-25	1
	Month 4	2	81.5	27.58	81.5	62	101	2	-9.0	16.97	-9.0	-21	3
	Month 6	2	97.0	7.07	97.0	92	102	2	6.5	17.68	6.5	-6	19
Overall	Baseline	10	81.1	10.86	82.5	64	98						
	Day 0	10	82.2	18.74	84.5	49	106	10	1.1	13.88	3.0	-25	20
	Day 0-Pre-dose	10	81.8	18.82	84.5	49	106	10	0.7	13.32	3.0	-24	20
	Day 0-15min Post	10	83.1	14.07	80.0	65	111	10	2.0	11.79	1.0	-14	22
	Day 0-1hr Post	10	86.6	16.97	87.5	51	117	10	5.5	12.54	3.5	-13	32
	Day 0-4hr Post	10	81.4	19.30	76.0	53	115	10	0.3	15.64	-3.5	-17	30

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline includes only those subjects with both a baseline value and a value for then summarized time period.

Cross Reference: Listing 16.2.9

Table 14.3.4.5 Summary of Vital Signs
Systolic Blood Pressure (mmHg)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Overall	Day 0-8hr Post	9	84.4	10.73	88.0	67	101	9	3.6	10.75	5.0	-15	16
	Day 0-12hr Post	10	76.0	13.27	77.5	51	98	10	-5.1	12.31	-7.5	-20	16
	Day 0-16hr Post	10	80.6	14.14	86.5	52	94	10	-0.5	12.89	3.0	-23	18
	Day 0-20hr Post	10	85.7	11.45	85.5	69	100	10	4.6	9.99	6.0	-12	20
	Day 0-24hr Post	1	98.0		98.0	98	98	1	0.0		0.0	0	0
	Day 1	10	81.8	12.63	83.5	62	100	10	0.7	8.74	-2.0	-11	20
	Day 4	10	84.2	16.61	80.5	62	108	10	3.1	10.76	6.5	-18	21
	Day 4-Pre-dose	10	84.2	16.61	80.5	62	108	10	3.1	10.76	6.5	-18	21
	Day 4-15min Post	10	83.8	12.54	83.0	60	107	10	2.7	8.01	0.5	-10	14
	Day 4-1hr Post	10	90.1	12.14	89.0	66	108	10	9.0	6.09	7.5	2	18
	Day 4-4hr Post	10	82.7	14.06	85.5	54	99	10	1.6	13.01	4.0	-19	21
	Day 4-8hr Post	9	81.8	10.49	85.0	63	93	9	2.0	11.52	7.0	-21	12
	Day 4-12hr Post	10	81.4	11.58	81.0	60	100	10	0.3	11.08	1.5	-23	18
	Day 4-16hr Post	9	83.9	15.84	79.0	65	109	9	2.1	15.92	-4.0	-16	32
	Day 4-20hr Post	9	84.3	17.41	82.0	56	112	9	2.6	12.91	4.0	-26	15
	Day 4-24hr Post	2	82.0	8.49	82.0	76	88	2	-8.5	2.12	-8.5	-10	-7
	Day 7	10	79.0	11.72	76.5	66	94	10	-2.1	10.67	-1.5	-17	19
	Day 7-Pre-dose	10	78.1	12.94	76.5	59	94	10	-3.0	10.57	-5.0	-17	19
	Day 7-15min Post	10	80.5	15.34	83.5	57	100	10	-0.6	11.71	1.5	-25	12
	Day 7-1hr Post	10	85.4	16.13	84.5	59	114	10	4.3	15.06	4.5	-17	29
	Day 7-4hr Post	10	94.6	16.97	92.0	71	119	10	13.5	13.60	18.0	-11	33
	Day 7-8hr Post	10	74.3	14.86	71.5	55	101	10	-6.8	11.86	-2.5	-25	8
	Day 7-12hr Post	10	83.1	9.24	86.0	68	93	10	2.0	7.53	3.5	-8	11
	Day 7-16hr Post	10	83.3	9.71	83.0	72	103	10	2.2	13.55	0.5	-21	23
	Day 7-20hr Post	10	81.9	13.07	80.5	62	103	10	0.8	13.29	1.5	-20	18
	Day 7-24hr Post	2	86.0	26.87	86.0	67	105	2	-4.5	16.26	-4.5	-16	7
	Day 11	10	83.8	14.68	85.0	66	105	10	2.7	12.44	4.0	-18	20
	Day 11-Pre-dose	10	84.5	15.17	85.0	66	105	10	3.4	13.37	4.0	-18	22
	Day 11-15min Post	10	82.4	14.53	80.5	66	103	10	1.3	13.55	3.0	-15	17
	Day 11-1hr Post	10	83.5	14.28	83.5	63	107	10	2.4	13.47	-3.5	-13	22
	Day 11-4hr Post	10	91.9	18.35	91.5	69	128	10	10.8	16.12	15.5	-17	35
	Day 11-8hr Post	10	88.8	22.42	92.0	58	124	10	7.7	16.71	6.5	-17	38
	Day 11-12hr Post	9	79.3	11.59	78.0	62	94	9	-1.6	11.01	-1.0	-20	14
	Day 11-16hr Post	9	80.8	15.23	78.0	62	105	9	-0.1	15.80	0.0	-20	30

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline includes only those subjects with both a baseline value and a value for then summarized time period.

Cross Reference: Listing 16.2.9

Table 14.3.4.5 Summary of Vital Signs
Systolic Blood Pressure (mmHg)

		Actual Values						Change From Baseline				
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Overall	Day 11-20hr Post	10	85.2	11.32	84.0	65	108	10	4.1	5.51	2.0	-4	14
	Day 11-24hr Post	2	94.0	7.07	94.0	89	99	2	3.5	3.54	3.5	1	6
	Day 14	10	91.5	13.29	88.0	73	115	10	10.4	7.37	10.5	1	22
	Day 14-Pre-dose	9	92.8	13.03	90.0	77	115	9	12.1	6.90	14.0	2	22
	Day 14-15min Post	9	83.7	11.59	83.0	69	105	9	3.0	12.00	1.0	-14	20
	Day 14-1hr Post	9	89.0	12.45	90.0	69	115	9	8.3	12.85	5.0	-4	32
	Day 14-4hr Post	10	89.9	15.39	87.0	68	116	10	8.8	12.88	7.0	-7	28
	Day 14-8hr Post	10	86.2	14.01	84.0	69	109	10	5.1	13.21	3.0	-14	25
	Day 14-12hr Post	10	87.1	15.09	85.5	71	123	10	6.0	17.71	2.5	-26	37
	Day 14-16hr Post	10	88.2	15.74	83.5	74	127	10	7.1	18.52	6.5	-24	44
	Day 14-20hr Post	10	83.0	6.94	85.0	68	91	10	1.9	8.23	2.5	-12	14
	Day 14-24hr Post	1	79.0		79.0	79	79	1	-19.0		-19.0	-19	-19
	Day 15	9	82.1	5.82	81.0	74	91	9	1.4	13.68	1.0	-24	19
	Day 21	10	82.1	9.96	79.5	68	102	10	1.0	10.64	-5.0	-9	17
	Month 2	10	82.6	11.50	84.0	58	99	10	1.5	14.47	0.0	-25	26
	Month 4	10	95.3	14.02	99.0	62	110	10	14.2	17.76	11.5	-21	41
	Month 6	10	100.5	12.02	102.5	82	116	10	19.4	13.70	19.0	-6	39
Siblings	Enrollment	4	95.5	4.43	95.0	91	101						

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline includes only those subjects with both a baseline value and a value for then summarized time period.

Cross Reference: Listing 16.2.9

Table 14.3.4.5 Summary of Vital Signs

Diastolic Blood Pressure (mmHg)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Baseline	3	59.0	11.53	58.0	48	71						
	Day 0	3	60.0	9.85	63.0	49	68	3	1.0	4.00	1.0	-3	5
	Day 0-Pre-dose	3	61.7	7.09	63.0	54	68	3	2.7	4.93	5.0	-3	6
	Day 0-15min Post	3	56.3	29.69	49.0	31	89	3	-2.7	22.72	1.0	-27	18
	Day 0-1hr Post	3	55.7	12.90	52.0	45	70	3	-3.3	8.74	-1.0	-13	4
	Day 0-4hr Post	3	37.0	5.20	40.0	31	40	3	-22.0	7.81	-18.0	-31	-17
	Day 0-8hr Post	3	52.0	12.53	51.0	40	65	3	-7.0	10.54	-6.0	-18	3
	Day 0-12hr Post	3	52.0	9.17	54.0	42	60	3	-7.0	19.16	2.0	-29	6
	Day 0-16hr Post	3	48.3	6.11	47.0	43	55	3	-10.7	8.39	-15.0	-16	-1
	Day 0-20hr Post	3	53.3	12.34	50.0	43	67	3	-5.7	8.62	-4.0	-15	2
	Day 1	3	52.3	12.86	47.0	43	67	3	-6.7	7.37	-4.0	-15	-1
	Day 4	3	50.3	11.15	46.0	42	63	3	-8.7	7.02	-8.0	-16	-2
	Day 4-Pre-dose	3	50.3	11.15	46.0	42	63	3	-8.7	7.02	-8.0	-16	-2
	Day 4-15min Post	3	58.7	24.70	55.0	36	85	3	-0.3	19.09	7.0	-22	14
	Day 4-1hr Post	3	49.0	9.00	49.0	40	58	3	-10.0	9.85	-13.0	-18	1
	Day 4-4hr Post	3	49.0	4.00	49.0	45	53	3	-10.0	14.18	-5.0	-26	1
	Day 4-8hr Post	2	61.5	7.78	61.5	56	67	2	8.5	14.85	8.5	-2	19
	Day 4-12hr Post	3	54.7	5.86	57.0	48	59	3	-4.3	6.66	-1.0	-12	0
	Day 4-16hr Post	3	58.7	5.77	62.0	52	62	3	-0.3	12.50	-6.0	-9	14
	Day 4-20hr Post	3	49.0	11.79	52.0	36	59	3	-10.0	21.70	1.0	-35	4
	Day 7	3	49.3	4.93	47.0	46	55	3	-9.7	7.09	-11.0	-16	-2
	Day 7-Pre-dose	3	49.3	4.93	47.0	46	55	3	-9.7	7.09	-11.0	-16	-2
	Day 7-15min Post	3	51.7	17.01	45.0	39	71	3	-7.3	19.55	-9.0	-26	13
	Day 7-1hr Post	3	58.0	6.93	54.0	54	66	3	-1.0	13.89	6.0	-17	8
	Day 7-4hr Post	3	62.3	10.97	56.0	56	75	3	3.3	5.03	4.0	-2	8
	Day 7-8hr Post	3	50.3	2.31	49.0	49	53	3	-8.7	13.50	-9.0	-22	5
	Day 7-12hr Post	3	43.0	7.21	45.0	35	49	3	-16.0	14.80	-23.0	-26	1
	Day 7-16hr Post	3	44.0	4.36	42.0	41	49	3	-15.0	8.19	-17.0	-22	-6
	Day 7-20hr Post	3	47.0	2.65	46.0	45	50	3	-12.0	12.49	-8.0	-26	-2
	Day 11	3	50.3	16.07	57.0	32	62	3	-8.7	11.02	-14.0	-16	4
	Day 11-Pre-dose	3	50.3	16.07	57.0	32	62	3	-8.7	11.02	-14.0	-16	4
	Day 11-15min Post	3	46.3	17.62	41.0	32	66	3	-12.7	19.22	-16.0	-30	8
	Day 11-1hr Post	3	57.3	15.04	56.0	43	73	3	-1.7	3.51	-2.0	-5	2
	Day 11-4hr Post	3	53.3	3.21	52.0	51	57	3	-5.7	8.50	-6.0	-14	3

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline includes only those subjects with both a baseline value and a value for then summarized time period.

Cross Reference: Listing 16.2.9

Table 14.3.4.5 Summary of Vital Signs
Diastolic Blood Pressure (mmHg)

		Actual Values						Change From Baseline				
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Day 11-8hr Post	3	57.7	26.63	51.0	35	87	3	-1.3	26.50	-13.0	-20	29
	Day 11-12hr Post	3	44.0	7.55	43.0	37	52	3	-15.0	4.00	-15.0	-19	-11
	Day 11-16hr Post	3	62.3	16.04	61.0	47	79	3	3.3	15.95	-1.0	-10	21
	Day 11-20hr Post	3	47.3	5.13	46.0	43	53	3	-11.7	8.50	-15.0	-18	-2
	Day 14	3	42.3	10.12	37.0	36	54	3	-16.7	5.51	-17.0	-22	-11
	Day 14-Pre-dose	3	43.7	9.29	41.0	36	54	3	-15.3	7.64	-17.0	-22	-7
	Day 14-15min Post	3	42.7	2.52	43.0	40	45	3	-16.3	9.07	-15.0	-26	-8
	Day 14-1hr Post	3	37.0	4.36	39.0	32	40	3	-22.0	7.94	-19.0	-31	-16
	Day 14-4hr Post	3	51.3	15.01	52.0	36	66	3	-7.7	3.79	-6.0	-12	-5
	Day 14-8hr Post	3	35.7	8.33	33.0	29	45	3	-23.3	13.05	-19.0	-38	-13
	Day 14-12hr Post	3	48.3	9.07	47.0	40	58	3	-10.7	12.22	-8.0	-24	0
	Day 14-16hr Post	3	39.0	3.61	38.0	36	43	3	-20.0	15.00	-20.0	-35	-5
	Day 14-20hr Post	3	40.7	6.11	42.0	34	46	3	-18.3	17.62	-16.0	-37	-2
	Day 15	3	44.7	11.59	43.0	34	57	3	-14.3	19.73	-5.0	-37	-1
	Day 21	3	41.3	6.11	40.0	36	48	3	-17.7	8.39	-22.0	-23	-8
	Month 2	3	56.3	24.58	48.0	37	84	3	-2.7	13.58	-10.0	-11	13
	Month 4	3	52.7	1.53	53.0	51	54	3	-6.3	10.07	-5.0	-17	3
	Month 6	3	70.0	16.09	68.0	55	87	3	11.0	16.37	7.0	-3	29
Cohort 2	Baseline	5	50.4	7.06	47.0	44	59						
	Day 0	5	46.2	12.60	50.0	27	59	5	-4.2	9.65	-3.0	-20	6
	Day 0-Pre-dose	5	46.2	12.60	50.0	27	59	5	-4.2	9.65	-3.0	-20	6
	Day 0-15min Post	5	51.6	13.05	44.0	40	71	5	1.2	15.21	-3.0	-13	27
	Day 0-1hr Post	5	52.2	13.95	52.0	33	67	5	1.8	13.77	0.0	-14	23
	Day 0-4hr Post	5	48.6	13.87	40.0	37	67	5	-1.8	13.61	-7.0	-18	16
	Day 0-8hr Post	5	51.2	13.59	56.0	32	66	5	0.8	15.22	0.0	-14	22
	Day 0-12hr Post	5	45.4	12.42	46.0	29	62	5	-5.0	13.82	-6.0	-18	18
	Day 0-16hr Post	5	52.0	20.26	58.0	27	77	5	1.6	19.79	1.0	-20	33
	Day 0-20hr Post	5	52.4	13.41	53.0	37	73	5	2.0	15.28	-3.0	-8	29
	Day 1	5	52.2	13.70	53.0	36	73	5	1.8	15.45	-3.0	-9	29
	Day 4	5	46.6	6.47	46.0	38	56	5	-3.8	5.63	-3.0	-12	3
	Day 4-Pre-dose	5	45.4	7.33	46.0	38	56	5	-5.0	7.97	-3.0	-18	3
	Day 4-15min Post	5	39.8	5.85	38.0	32	47	5	-10.6	12.01	-6.0	-27	2
	Day 4-1hr Post	5	47.0	5.52	45.0	40	54	5	-3.4	6.47	-4.0	-12	6

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline includes only those subjects with both a baseline value and a value for then summarized time period.

Cross Reference: Listing 16.2.9

Table 14.3.4.5 Summary of Vital Signs
Diastolic Blood Pressure (mmHg)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 2	Day 4-4hr Post	5	49.0	19.95	50.0	26	71	5	-1.4	18.73	-7.0	-19	27
	Day 4-8hr Post	5	45.4	15.32	42.0	30	66	5	-5.0	14.23	-14.0	-17	12
	Day 4-12hr Post	5	42.6	7.89	44.0	33	51	5	-7.8	8.04	-9.0	-15	5
	Day 4-16hr Post	4	40.8	11.24	39.0	29	56	4	-11.3	12.92	-7.0	-30	-1
	Day 4-20hr Post	4	36.0	11.63	39.0	20	46	4	-16.0	6.38	-14.0	-25	-11
	Day 7	5	39.6	7.02	38.0	34	51	5	-10.8	10.50	-13.0	-19	7
	Day 7-Pre-dose	5	39.6	7.02	38.0	34	51	5	-10.8	10.50	-13.0	-19	7
	Day 7-15min Post	5	46.2	10.78	43.0	36	62	5	-4.2	5.40	-5.0	-11	3
	Day 7-1hr Post	5	50.2	23.22	48.0	28	86	5	-0.2	19.42	-9.0	-19	27
	Day 7-4hr Post	5	52.6	14.71	54.0	37	75	5	2.2	10.26	-2.0	-10	16
	Day 7-8hr Post	5	40.6	8.73	45.0	28	48	5	-9.8	8.14	-12.0	-17	4
	Day 7-12hr Post	5	51.8	8.79	51.0	39	61	5	1.4	10.19	4.0	-10	14
	Day 7-16hr Post	5	41.8	5.93	39.0	35	49	5	-8.6	11.99	-6.0	-22	5
	Day 7-20hr Post	5	39.2	10.06	36.0	30	56	5	-11.2	13.50	-15.0	-23	12
	Day 11	5	48.6	11.99	50.0	32	64	5	-1.8	13.85	5.0	-25	9
	Day 11-Pre-dose	5	49.6	12.34	54.0	32	64	5	-0.8	14.70	5.0	-25	11
	Day 11-15min Post	5	48.6	20.04	40.0	32	83	5	-1.8	16.45	-7.0	-17	24
	Day 11-1hr Post	5	43.6	17.27	36.0	28	72	5	-6.8	14.50	-11.0	-22	13
	Day 11-4hr Post	5	45.8	11.26	51.0	29	57	5	-4.6	12.92	-8.0	-17	10
	Day 11-8hr Post	5	32.0	4.30	34.0	25	36	5	-18.4	5.50	-20.0	-23	-10
	Day 11-12hr Post	5	39.4	10.19	38.0	26	50	5	-11.0	11.20	-10.0	-23	6
	Day 11-16hr Post	5	41.2	15.32	34.0	26	63	5	-9.2	14.11	-13.0	-25	7
	Day 11-20hr Post	5	45.6	9.40	42.0	37	58	5	-4.8	10.62	-6.0	-15	13
	Day 14	5	45.0	6.20	46.0	36	53	5	-5.4	9.42	-4.0	-21	2
	Day 14-Pre-dose	4	43.0	4.97	44.5	36	47	4	-5.3	10.87	-1.0	-21	2
	Day 14-15min Post	4	40.8	9.98	40.0	30	53	4	-7.5	15.35	-6.0	-27	9
	Day 14-1hr Post	4	42.8	6.65	42.5	37	49	4	-5.5	5.80	-7.5	-10	3
	Day 14-4hr Post	5	41.8	5.50	41.0	34	48	5	-8.6	11.67	-7.0	-23	3
	Day 14-8hr Post	5	50.6	11.28	54.0	35	61	5	0.2	14.81	-5.0	-14	16
	Day 14-12hr Post	5	45.8	9.83	49.0	31	54	5	-4.6	13.13	-3.0	-26	9
	Day 14-16hr Post	5	39.4	10.48	36.0	30	52	5	-11.0	10.30	-15.0	-21	5
	Day 14-20hr Post	5	52.6	13.58	49.0	36	72	5	2.2	11.82	2.0	-11	15
	Day 15	4	36.3	8.96	33.0	30	49	4	-12.0	11.60	-16.0	-21	5
	Day 21	5	45.2	13.70	42.0	31	68	5	-5.2	12.76	-3.0	-26	9

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline includes only those subjects with both a baseline value and a value for then summarized time period.

Cross Reference: Listing 16.2.9

Table 14.3.4.5 Summary of Vital Signs
Diastolic Blood Pressure (mmHg)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 2	Month 2	5	40.8	7.36	43.0	33	48	5	-9.6	10.50	-9.0	-26	0
	Month 4	5	56.0	8.51	57.0	43	66	5	5.6	8.08	7.0	-3	16
	Month 6	5	56.0	6.89	55.0	48	67	5	5.6	7.30	10.0	-5	12
Cohort 3	Baseline	2	62.5	19.09	62.5	49	76						
	Day 0	2	44.0	15.56	44.0	33	55	2	-18.5	3.54	-18.5	-21	-16
	Day 0-Pre-dose	2	44.0	15.56	44.0	33	55	2	-18.5	3.54	-18.5	-21	-16
	Day 0-15min Post	2	44.5	16.26	44.5	33	56	2	-18.0	2.83	-18.0	-20	-16
	Day 0-1hr Post	2	48.5	17.68	48.5	36	61	2	-14.0	1.41	-14.0	-15	-13
	Day 0-4hr Post	2	56.0	2.83	56.0	54	58	2	-6.5	16.26	-6.5	-18	5
	Day 0-8hr Post	1	52.0		52.0	52	52	1	-24.0		-24.0	-24	-24
	Day 0-12hr Post	2	52.5	2.12	52.5	51	54	2	-10.0	16.97	-10.0	-22	2
	Day 0-16hr Post	2	56.0	2.83	56.0	54	58	2	-6.5	21.92	-6.5	-22	9
	Day 0-20hr Post	2	47.5	12.02	47.5	39	56	2	-15.0	7.07	-15.0	-20	-10
	Day 0-24hr Post	1	55.0		55.0	55	55	1	-21.0		-21.0	-21	-21
	Day 1	2	43.0	18.38	43.0	30	56	2	-19.5	0.71	-19.5	-20	-19
	Day 4	2	50.0	25.46	50.0	32	68	2	-12.5	6.36	-12.5	-17	-8
	Day 4-Pre-dose	2	50.0	25.46	50.0	32	68	2	-12.5	6.36	-12.5	-17	-8
	Day 4-15min Post	2	42.0	16.97	42.0	30	54	2	-20.5	2.12	-20.5	-22	-19
	Day 4-1hr Post	2	66.5	20.51	66.5	52	81	2	4.0	1.41	4.0	3	5
	Day 4-4hr Post	2	48.0	2.83	48.0	46	50	2	-14.5	21.92	-14.5	-30	1
	Day 4-8hr Post	2	43.0	7.07	43.0	38	48	2	-19.5	26.16	-19.5	-38	-1
	Day 4-12hr Post	2	49.5	2.12	49.5	48	51	2	-13.0	16.97	-13.0	-25	-1
	Day 4-16hr Post	2	65.5	17.68	65.5	53	78	2	3.0	1.41	3.0	2	4
	Day 4-20hr Post	2	76.0	21.21	76.0	61	91	2	13.5	2.12	13.5	12	15
	Day 4-24hr Post	2	56.5	21.92	56.5	41	72	2	-6.0	2.83	-6.0	-8	-4
	Day 7	2	40.5	17.68	40.5	28	53	2	-22.0	1.41	-22.0	-23	-21
	Day 7-Pre-dose	2	40.5	17.68	40.5	28	53	2	-22.0	1.41	-22.0	-23	-21
	Day 7-15min Post	2	53.0	4.24	53.0	50	56	2	-9.5	14.85	-9.5	-20	1
	Day 7-1hr Post	2	62.5	7.78	62.5	57	68	2	0.0	11.31	0.0	-8	8
	Day 7-4hr Post	2	65.5	36.06	65.5	40	91	2	3.0	16.97	3.0	-9	15
	Day 7-8hr Post	2	39.5	16.26	39.5	28	51	2	-23.0	2.83	-23.0	-25	-21
	Day 7-12hr Post	2	39.5	7.78	39.5	34	45	2	-23.0	11.31	-23.0	-31	-15
	Day 7-16hr Post	2	39.5	6.36	39.5	35	44	2	-23.0	25.46	-23.0	-41	-5

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline includes only those subjects with both a baseline value and a value for then summarized time period.

Cross Reference: Listing 16.2.9

Table 14.3.4.5 Summary of Vital Signs
Diastolic Blood Pressure (mmHg)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 3	Day 7-20hr Post	2	66.5	13.44	66.5	57	76	2	4.0	5.66	4.0	0	8
	Day 7-24hr Post	2	65.5	31.82	65.5	43	88	2	3.0	12.73	3.0	-6	12
	Day 11	2	37.0	11.31	37.0	29	45	2	-25.5	7.78	-25.5	-31	-20
	Day 11-Pre-dose	2	37.0	11.31	37.0	29	45	2	-25.5	7.78	-25.5	-31	-20
	Day 11-15min Post	2	41.5	0.71	41.5	41	42	2	-21.0	18.38	-21.0	-34	-8
	Day 11-1hr Post	2	50.5	3.54	50.5	48	53	2	-12.0	15.56	-12.0	-23	-1
	Day 11-4hr Post	2	58.5	9.19	58.5	52	65	2	-4.0	9.90	-4.0	-11	3
	Day 11-8hr Post	2	56.5	2.12	56.5	55	58	2	-6.0	21.21	-6.0	-21	9
	Day 11-12hr Post	1	43.0		43.0	43	43	1	-33.0		-33.0	-33	-33
	Day 11-16hr Post	1	64.0		64.0	64	64	1	-12.0		-12.0	-12	-12
	Day 11-20hr Post	2	61.0	21.21	61.0	46	76	2	-1.5	2.12	-1.5	-3	0
	Day 11-24hr Post	2	67.0	18.38	67.0	54	80	2	4.5	0.71	4.5	4	5
	Day 14	2	56.0	5.66	56.0	52	60	2	-6.5	24.75	-6.5	-24	11
	Day 14-Pre-dose	2	56.0	5.66	56.0	52	60	2	-6.5	24.75	-6.5	-24	11
	Day 14-15min Post	2	72.0	22.63	72.0	56	88	2	9.5	3.54	9.5	7	12
	Day 14-1hr Post	2	68.0	2.83	68.0	66	70	2	5.5	21.92	5.5	-10	21
	Day 14-4hr Post	2	72.0	4.24	72.0	69	75	2	9.5	23.33	9.5	-7	26
	Day 14-8hr Post	2	52.5	6.36	52.5	48	57	2	-10.0	25.46	-10.0	-28	8
	Day 14-12hr Post	2	52.0	4.24	52.0	49	55	2	-10.5	14.85	-10.5	-21	0
	Day 14-16hr Post	2	66.0	18.38	66.0	53	79	2	3.5	37.48	3.5	-23	30
	Day 14-20hr Post	2	51.0	8.49	51.0	45	57	2	-11.5	10.61	-11.5	-19	-4
	Day 14-24hr Post	1	65.0		65.0	65	65	1	-11.0		-11.0	-11	-11
	Day 15	2	51.0	2.83	51.0	49	53	2	-11.5	16.26	-11.5	-23	0
	Day 21	2	50.0	4.24	50.0	47	53	2	-12.5	14.85	-12.5	-23	-2
	Month 2	2	51.5	31.82	51.5	29	74	2	-11.0	12.73	-11.0	-20	-2
	Month 4	2	53.5	10.61	53.5	46	61	2	-9.0	8.49	-9.0	-15	-3
	Month 6	2	60.5	2.12	60.5	59	62	2	-2.0	21.21	-2.0	-17	13
Overall	Baseline	10	55.4	11.03	53.0	44	76						
	Day 0	10	49.9	12.97	52.0	27	68	10	-5.5	9.95	-3.0	-21	6
	Day 0-Pre-dose	10	50.4	13.03	54.0	27	68	10	-5.0	10.42	-3.0	-21	6
	Day 0-15min Post	10	51.6	17.88	46.5	31	89	10	-3.8	16.66	-4.0	-27	27
	Day 0-1hr Post	10	52.5	12.85	52.0	33	70	10	-2.9	11.88	-3.0	-15	23
	Day 0-4hr Post	10	46.6	12.04	40.0	31	67	10	-8.8	14.55	-12.5	-31	16

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline includes only those subjects with both a baseline value and a value for then summarized time period.

Cross Reference: Listing 16.2.9

Table 14.3.4.5 Summary of Vital Signs
Diastolic Blood Pressure (mmHg)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Overall	Day 0-8hr Post	9	51.6	11.48	52.0	32	66	9	-4.6	14.53	-6.0	-24	22
	Day 0-12hr Post	10	48.8	10.03	51.0	29	62	10	-6.6	14.23	-6.0	-29	18
	Day 0-16hr Post	10	51.7	14.13	54.5	27	77	10	-3.7	16.63	-5.0	-22	33
	Day 0-20hr Post	10	51.7	11.61	51.5	37	73	10	-3.7	13.17	-5.0	-20	29
	Day 0-24hr Post	1	55.0		55.0	55	55	1	-21.0		-21.0	-21	-21
	Day 1	10	50.4	13.15	50.0	30	73	10	-5.0	13.84	-5.0	-20	29
	Day 4	10	48.4	11.04	46.0	32	68	10	-7.0	6.55	-7.0	-17	3
	Day 4-Pre-dose	10	47.8	11.40	46.0	32	68	10	-7.6	7.29	-7.0	-18	3
	Day 4-15min Post	10	45.9	16.16	41.0	30	85	10	-9.5	14.18	-12.5	-27	14
	Day 4-1hr Post	10	51.5	11.90	50.0	40	81	10	-3.9	8.17	-3.0	-18	6
	Day 4-4hr Post	10	48.8	13.47	49.5	26	71	10	-6.6	16.93	-6.0	-30	27
	Day 4-8hr Post	9	48.4	13.68	48.0	30	67	9	-5.2	17.68	-2.0	-38	19
	Day 4-12hr Post	10	47.6	8.19	48.5	33	59	10	-7.8	8.98	-7.5	-25	5
	Day 4-16hr Post	9	52.2	14.84	53.0	29	78	9	-4.4	12.05	-5.0	-30	14
	Day 4-20hr Post	9	49.2	20.21	46.0	20	91	9	-7.4	16.80	-11.0	-35	15
	Day 4-24hr Post	2	56.5	21.92	56.5	41	72	2	-6.0	2.83	-6.0	-8	-4
	Day 7	10	42.7	9.12	43.5	28	55	10	-12.7	9.20	-14.5	-23	7
	Day 7-Pre-dose	10	42.7	9.12	43.5	28	55	10	-12.7	9.20	-14.5	-23	7
	Day 7-15min Post	10	49.2	11.32	47.5	36	71	10	-6.2	11.29	-6.0	-26	13
	Day 7-1hr Post	10	55.0	16.89	55.5	28	86	10	-0.4	15.00	-1.0	-19	27
	Day 7-4hr Post	10	58.1	17.39	55.5	37	91	10	2.7	9.20	1.0	-10	16
	Day 7-8hr Post	10	43.3	9.39	47.5	28	53	10	-12.1	10.20	-13.0	-25	5
	Day 7-12hr Post	10	46.7	9.12	47.0	34	61	10	-8.7	15.13	-9.0	-31	14
	Day 7-16hr Post	10	42.0	5.21	41.5	35	49	10	-13.4	13.60	-11.5	-41	5
	Day 7-20hr Post	10	47.0	13.60	45.5	30	76	10	-8.4	12.73	-10.5	-26	12
	Day 7-24hr Post	2	65.5	31.82	65.5	43	88	2	3.0	12.73	3.0	-6	12
	Day 11	10	46.8	12.76	47.5	29	64	10	-8.6	14.42	-9.0	-31	9
	Day 11-Pre-dose	10	47.3	13.00	49.5	29	64	10	-8.1	15.06	-9.0	-31	11
	Day 11-15min Post	10	46.5	15.99	41.0	32	83	10	-8.9	17.47	-10.5	-34	24
	Day 11-1hr Post	10	49.1	14.97	47.5	28	73	10	-6.3	11.73	-3.5	-23	13
	Day 11-4hr Post	10	50.6	9.86	52.0	29	65	10	-4.8	10.08	-7.0	-17	10
	Day 11-8hr Post	10	44.6	18.52	35.5	25	87	10	-10.8	16.93	-18.0	-23	29
	Day 11-12hr Post	9	41.3	8.46	43.0	26	52	9	-14.8	10.83	-15.0	-33	6
	Day 11-16hr Post	9	50.8	17.63	51.0	26	79	9	-5.3	14.36	-10.0	-25	21

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Baseline value is the last value taken prior to study drug administration.
Change from baseline includes only those subjects with both a baseline value and a value for then summarized time period.

Cross Reference: Listing 16.2.9

Table 14.3.4.5 Summary of Vital Signs
Diastolic Blood Pressure (mmHg)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Overall	Day 11-20hr Post	10	49.2	11.59	46.0	37	76	10	-6.2	9.09	-6.0	-18	13
	Day 11-24hr Post	2	67.0	18.38	67.0	54	80	2	4.5	0.71	4.5	4	5
	Day 14	10	46.4	8.40	46.5	36	60	10	-9.0	11.94	-8.5	-24	11
	Day 14-Pre-dose	9	46.1	8.15	46.0	36	60	9	-8.9	12.61	-7.0	-24	11
	Day 14-15min Post	9	48.3	16.84	44.0	30	88	9	-6.7	14.53	-8.0	-27	12
	Day 14-1hr Post	9	46.4	13.37	40.0	32	70	9	-8.6	14.50	-10.0	-31	21
	Day 14-4hr Post	10	50.7	14.51	47.0	34	75	10	-4.7	13.43	-6.5	-23	26
	Day 14-8hr Post	10	46.5	11.53	46.5	29	61	10	-8.9	17.97	-12.5	-38	16
	Day 14-12hr Post	10	47.8	8.34	49.0	31	58	10	-7.6	12.01	-4.0	-26	9
	Day 14-16hr Post	10	44.6	14.71	40.5	30	79	10	-10.8	18.08	-16.0	-35	30
	Day 14-20hr Post	10	48.7	11.37	46.5	34	72	10	-6.7	15.42	-6.0	-37	15
	Day 14-24hr Post	1	65.0		65.0	65	65	1	-11.0		-11.0	-11	-11
	Day 15	9	42.3	10.20	43.0	30	57	9	-12.7	13.51	-15.0	-37	5
	Day 21	10	45.0	10.19	43.0	31	68	10	-10.4	12.08	-6.0	-26	9
	Month 2	10	47.6	18.04	45.0	29	84	10	-7.8	10.99	-9.5	-26	13
	Month 4	10	54.5	6.92	54.0	43	66	10	-0.9	10.37	-2.5	-17	16
	Month 6	10	61.1	10.96	57.5	48	87	10	5.7	12.48	8.5	-17	29
Siblings	Enrollment	4	54.3	4.27	54.5	49	59						

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Cross Reference: Listing 16.2.9

Table 14.3.4.5 Summary of Vital Signs

Respiration Rate (breaths/min)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Baseline	3	45.7	3.79	44.0	43	50						
	Day 0	3	42.7	1.53	43.0	41	44	3	-3.0	5.20	0.0	-9	0
	Day 0-Pre-dose	3	42.0	1.73	41.0	41	44	3	-3.7	4.73	-2.0	-9	0
	Day 0-15min Post	3	43.7	5.51	44.0	38	49	3	-2.0	2.65	-1.0	-5	0
	Day 0-1hr Post	3	49.7	12.50	44.0	41	64	3	4.0	8.72	0.0	-2	14
	Day 0-4hr Post	3	49.7	6.43	47.0	45	57	3	4.0	3.00	4.0	1	7
	Day 0-8hr Post	3	49.7	9.07	46.0	43	60	3	4.0	5.29	2.0	0	10
	Day 0-12hr Post	3	38.3	1.53	38.0	37	40	3	-7.3	2.31	-6.0	-10	-6
	Day 0-16hr Post	3	50.3	8.50	50.0	42	59	3	4.7	9.87	0.0	-2	16
	Day 0-20hr Post	3	49.0	11.53	48.0	38	61	3	3.3	12.86	-2.0	-6	18
	Day 1	3	48.3	10.50	48.0	38	59	3	2.7	11.72	-2.0	-6	16
	Day 4	3	38.7	5.77	42.0	32	42	3	-7.0	5.57	-8.0	-12	-1
	Day 4-Pre-dose	3	38.7	5.77	42.0	32	42	3	-7.0	5.57	-8.0	-12	-1
	Day 4-15min Post	3	35.7	8.02	35.0	28	44	3	-10.0	5.29	-8.0	-16	-6
	Day 4-1hr Post	3	38.3	9.29	41.0	28	46	3	-7.3	7.57	-4.0	-16	-2
	Day 4-4hr Post	3	34.7	6.11	36.0	28	40	3	-11.0	7.00	-14.0	-16	-3
	Day 4-8hr Post	3	45.3	4.51	45.0	41	50	3	-0.3	5.69	-2.0	-5	6
	Day 4-12hr Post	3	42.0	8.72	46.0	32	48	3	-3.7	8.50	-4.0	-12	5
	Day 4-16hr Post	3	33.0	2.65	32.0	31	36	3	-12.7	1.53	-13.0	-14	-11
	Day 4-20hr Post	3	44.0	20.07	35.0	30	67	3	-1.7	22.90	-9.0	-20	24
	Day 7	3	43.7	3.51	44.0	40	47	3	-2.0	2.65	-3.0	-4	1
	Day 7-Pre-dose	3	41.7	4.73	40.0	38	47	3	-4.0	1.00	-4.0	-5	-3
	Day 7-15min Post	3	50.3	5.51	50.0	45	56	3	4.7	2.31	6.0	2	6
	Day 7-1hr Post	3	45.3	9.02	46.0	36	54	3	-0.3	12.66	2.0	-14	11
	Day 7-4hr Post	3	50.0	10.39	44.0	44	62	3	4.3	6.66	1.0	0	12
	Day 7-8hr Post	3	47.7	12.50	42.0	39	62	3	2.0	8.72	-2.0	-4	12
	Day 7-12hr Post	3	46.7	9.24	52.0	36	52	3	1.0	7.55	2.0	-7	8
	Day 7-16hr Post	3	43.0	7.00	43.0	36	50	3	-2.7	4.62	0.0	-8	0
	Day 7-20hr Post	3	45.7	7.37	43.0	40	54	3	0.0	4.00	0.0	-4	4
	Day 11	3	50.0	1.73	51.0	48	51	3	4.3	5.51	7.0	-2	8
	Day 11-Pre-dose	3	50.0	1.73	51.0	48	51	3	4.3	5.51	7.0	-2	8
	Day 11-15min Post	3	40.7	1.53	41.0	39	42	3	-5.0	2.65	-4.0	-8	-3
	Day 11-1hr Post	3	50.3	9.61	52.0	40	59	3	4.7	10.26	2.0	-4	16
	Day 11-4hr Post	3	41.0	1.73	40.0	40	43	3	-4.7	5.03	-4.0	-10	0

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Cross Reference: Listing 16.2.9

Table 14.3.4.5 Summary of Vital Signs
Respiration Rate (breaths/min)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 1	Day 11-8hr Post	3	40.7	6.03	40.0	35	47	3	-5.0	9.54	-4.0	-15	4
	Day 11-12hr Post	3	35.3	8.08	40.0	26	40	3	-10.3	11.85	-4.0	-24	-3
	Day 11-16hr Post	3	38.3	2.52	38.0	36	41	3	-7.3	4.51	-7.0	-12	-3
	Day 11-20hr Post	3	39.3	6.43	42.0	32	44	3	-6.3	10.21	-2.0	-18	1
	Day 14	3	43.0	3.00	43.0	40	46	3	-2.7	6.43	0.0	-10	2
	Day 14-Pre-dose	3	44.3	3.79	46.0	40	47	3	-1.3	7.57	2.0	-10	4
	Day 14-15min Post	3	49.7	10.69	44.0	43	62	3	4.0	6.93	0.0	0	12
	Day 14-1hr Post	3	43.0	11.53	47.0	30	52	3	-2.7	15.31	3.0	-20	9
	Day 14-4hr Post	3	39.7	2.89	38.0	38	43	3	-6.0	5.57	-5.0	-12	-1
	Day 14-8hr Post	3	45.0	16.09	47.0	28	60	3	-0.7	19.43	4.0	-22	16
	Day 14-12hr Post	3	42.7	8.33	40.0	36	52	3	-3.0	9.64	-7.0	-10	8
	Day 14-16hr Post	3	41.0	8.89	44.0	31	48	3	-4.7	12.66	0.0	-19	5
	Day 14-20hr Post	3	43.3	4.16	42.0	40	48	3	-2.3	7.09	-1.0	-10	4
	Day 15	3	46.0	5.29	48.0	40	50	3	0.3	8.96	5.0	-10	6
	Day 21	3	42.3	3.79	44.0	38	45	3	-3.3	3.79	-5.0	-6	1
	Month 2	3	30.3	5.69	32.0	24	35	3	-15.3	6.43	-18.0	-20	-8
	Month 4	3	29.3	9.24	24.0	24	40	3	-16.3	11.93	-20.0	-26	-3
	Month 6	3	26.3	3.79	28.0	22	29	3	-19.3	4.62	-22.0	-22	-14
Cohort 2	Baseline	5	47.2	12.05	45.0	33	61						
	Day 0	5	39.8	10.83	44.0	25	50	5	-7.4	9.91	-8.0	-17	9
	Day 0-Pre-dose	5	35.0	7.87	32.0	25	44	5	-12.2	4.55	-13.0	-17	-7
	Day 0-15min Post	5	43.4	9.63	46.0	30	55	5	-3.8	14.06	-3.0	-23	10
	Day 0-1hr Post	5	41.6	8.73	42.0	31	55	5	-5.6	19.63	-7.0	-30	22
	Day 0-4hr Post	5	40.2	8.35	44.0	29	49	5	-7.0	11.11	-9.0	-16	11
	Day 0-8hr Post	5	36.6	2.19	36.0	34	40	5	-10.6	13.01	-11.0	-24	7
	Day 0-12hr Post	5	42.0	9.87	43.0	30	52	5	-5.2	14.15	-9.0	-18	19
	Day 0-16hr Post	5	45.2	7.12	44.0	38	54	5	-2.0	13.06	0.0	-23	11
	Day 0-20hr Post	5	40.2	13.86	42.0	24	61	5	-7.0	12.00	-1.0	-21	3
	Day 1	5	38.2	7.95	42.0	24	42	5	-9.0	13.47	-16.0	-21	8
	Day 4	5	41.8	5.59	43.0	36	48	5	-5.4	11.26	-9.0	-15	13
	Day 4-Pre-dose	5	39.4	4.56	38.0	36	47	5	-7.8	10.38	-9.0	-20	7
	Day 4-15min Post	5	35.6	3.05	37.0	31	38	5	-11.6	12.82	-14.0	-24	5
	Day 4-1hr Post	5	34.0	6.28	32.0	29	45	5	-13.2	11.63	-13.0	-32	-1

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Cross Reference: Listing 16.2.9

Table 14.3.4.5 Summary of Vital Signs
Respiration Rate (breaths/min)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 2	Day 4-4hr Post	5	36.6	6.23	37.0	30	46	5	-10.6	10.16	-8.0	-26	-1
	Day 4-8hr Post	5	37.0	8.57	36.0	27	48	5	-10.2	15.35	-15.0	-25	15
	Day 4-12hr Post	5	36.2	5.36	35.0	29	42	5	-11.0	10.34	-4.0	-27	-4
	Day 4-16hr Post	4	43.3	3.77	44.5	38	46	4	-0.5	11.47	0.0	-15	13
	Day 4-20hr Post	4	39.5	12.61	41.5	23	52	4	-4.3	15.71	-4.0	-22	13
	Day 7	5	45.2	8.41	44.0	37	57	5	-2.0	13.91	-4.0	-20	17
	Day 7-Pre-dose	5	43.6	9.40	38.0	36	57	5	-3.6	13.35	-4.0	-20	17
	Day 7-15min Post	5	40.4	4.56	40.0	36	48	5	-6.8	14.36	-5.0	-22	9
	Day 7-1hr Post	5	38.6	11.59	35.0	31	59	5	-8.6	13.13	-7.0	-30	3
	Day 7-4hr Post	5	40.8	8.44	43.0	31	50	5	-6.4	15.06	-8.0	-28	14
	Day 7-8hr Post	5	33.4	3.71	34.0	30	39	5	-13.8	14.55	-15.0	-28	6
	Day 7-12hr Post	5	35.8	6.38	35.0	27	42	5	-11.4	15.65	-10.0	-34	9
	Day 7-16hr Post	5	36.0	5.92	33.0	31	45	5	-11.2	15.07	-14.0	-26	12
	Day 7-20hr Post	5	42.0	8.28	40.0	34	53	5	-5.2	13.29	1.0	-26	8
	Day 11	5	40.4	2.88	41.0	37	44	5	-6.8	14.52	-3.0	-24	8
	Day 11-Pre-dose	5	43.6	7.30	41.0	38	56	5	-3.6	16.04	5.0	-22	11
	Day 11-15min Post	5	43.6	9.24	40.0	35	54	5	-3.6	12.92	-3.0	-23	9
	Day 11-1hr Post	5	36.6	6.07	36.0	30	45	5	-10.6	10.14	-13.0	-25	1
	Day 11-4hr Post	5	45.2	8.07	40.0	38	54	5	-2.0	15.23	-4.0	-21	21
	Day 11-8hr Post	5	39.4	7.30	42.0	29	47	5	-7.8	15.75	-3.0	-32	8
	Day 11-12hr Post	5	37.0	13.19	32.0	23	58	5	-10.2	14.87	-3.0	-35	1
	Day 11-16hr Post	4	43.8	12.63	44.5	29	57	4	-5.5	25.27	-7.0	-32	24
	Day 11-20hr Post	4	43.5	11.33	46.0	29	53	4	-5.8	18.63	0.5	-32	8
	Day 14	5	39.6	3.85	40.0	34	44	5	-7.6	13.59	-11.0	-23	11
	Day 14-Pre-dose	5	40.8	4.82	42.0	34	46	5	-6.4	14.76	-11.0	-23	11
	Day 14-15min Post	5	38.4	6.73	39.0	32	48	5	-8.8	16.80	-13.0	-29	9
	Day 14-1hr Post	5	48.0	13.87	52.0	30	66	5	0.8	20.17	8.0	-31	20
	Day 14-4hr Post	5	43.4	7.70	43.0	36	55	5	-3.8	16.92	-3.0	-24	22
	Day 14-8hr Post	5	46.0	14.14	43.0	29	67	5	-1.2	15.40	4.0	-18	18
	Day 14-12hr Post	5	37.0	4.47	40.0	30	40	5	-10.2	16.16	-5.0	-31	7
	Day 14-16hr Post	5	36.6	6.47	35.0	30	46	5	-10.6	17.34	-15.0	-29	13
	Day 14-20hr Post	5	39.4	7.83	41.0	29	48	5	-7.8	15.24	-10.0	-27	12
	Day 15	5	39.8	11.12	35.0	30	55	5	-7.4	22.05	-15.0	-30	22
	Day 21	5	40.4	7.09	40.0	33	52	5	-6.8	14.17	-6.0	-24	7

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Cross Reference: Listing 16.2.9

Table 14.3.4.5 Summary of Vital Signs
Respiration Rate (breaths/min)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 2	Month 2	5	39.2	9.20	37.0	26	48	5	-8.0	16.58	-13.0	-24	15
	Month 4	4	43.5	4.73	42.0	40	50	4	-0.3	11.87	5.0	-18	7
	Month 6	5	39.4	6.77	36.0	32	48	5	-7.8	5.59	-9.0	-13	-1
Cohort 3	Baseline	2	47.0	4.24	47.0	44	50						
	Day 0	2	35.0	7.07	35.0	30	40	2	-12.0	11.31	-12.0	-20	-4
	Day 0-Pre-dose	2	35.0	7.07	35.0	30	40	2	-12.0	11.31	-12.0	-20	-4
	Day 0-15min Post	2	47.0	18.38	47.0	34	60	2	0.0	22.63	0.0	-16	16
	Day 0-1hr Post	2	33.5	2.12	33.5	32	35	2	-13.5	2.12	-13.5	-15	-12
	Day 0-4hr Post	2	43.5	0.71	43.5	43	44	2	-3.5	3.54	-3.5	-6	-1
	Day 0-8hr Post	1	37.0		37.0	37	37	1	-7.0		-7.0	-7	-7
	Day 0-12hr Post	2	35.5	4.95	35.5	32	39	2	-11.5	9.19	-11.5	-18	-5
	Day 0-16hr Post	2	40.0	0.00	40.0	40	40	2	-7.0	4.24	-7.0	-10	-4
	Day 0-20hr Post	2	49.5	12.02	49.5	41	58	2	2.5	16.26	2.5	-9	14
	Day 0-24hr Post	2	39.0	4.24	39.0	36	42	2	-8.0	8.49	-8.0	-14	-2
	Day 1	2	49.0	12.73	49.0	40	58	2	2.0	16.97	2.0	-10	14
	Day 4	2	55.0	4.24	55.0	52	58	2	8.0	0.00	8.0	8	8
	Day 4-Pre-dose	2	55.0	4.24	55.0	52	58	2	8.0	0.00	8.0	8	8
	Day 4-15min Post	2	36.0	2.83	36.0	34	38	2	-11.0	7.07	-11.0	-16	-6
	Day 4-1hr Post	2	43.0	7.07	43.0	38	48	2	-4.0	11.31	-4.0	-12	4
	Day 4-4hr Post	2	43.5	7.78	43.5	38	49	2	-3.5	12.02	-3.5	-12	5
	Day 4-8hr Post	2	39.0	1.41	39.0	38	40	2	-8.0	5.66	-8.0	-12	-4
	Day 4-12hr Post	2	41.5	6.36	41.5	37	46	2	-5.5	10.61	-5.5	-13	2
	Day 4-16hr Post	2	46.0	2.83	46.0	44	48	2	-1.0	1.41	-1.0	-2	0
	Day 4-20hr Post	2	40.5	2.12	40.5	39	42	2	-6.5	2.12	-6.5	-8	-5
	Day 4-24hr Post	2	39.0	4.24	39.0	36	42	2	-8.0	8.49	-8.0	-14	-2
	Day 7	2	53.0	1.41	53.0	52	54	2	6.0	2.83	6.0	4	8
	Day 7-Pre-dose	2	53.0	1.41	53.0	52	54	2	6.0	2.83	6.0	4	8
	Day 7-15min Post	2	53.0	7.07	53.0	48	58	2	6.0	2.83	6.0	4	8
	Day 7-1hr Post	2	52.0	5.66	52.0	48	56	2	5.0	1.41	5.0	4	6
	Day 7-4hr Post	2	43.5	12.02	43.5	35	52	2	-3.5	7.78	-3.5	-9	2
	Day 7-8hr Post	2	36.0	11.31	36.0	28	44	2	-11.0	15.56	-11.0	-22	0
	Day 7-12hr Post	2	46.0	2.83	46.0	44	48	2	-1.0	7.07	-1.0	-6	4
	Day 7-16hr Post	2	38.5	10.61	38.5	31	46	2	-8.5	14.85	-8.5	-19	2

n represents the number of subjects contributing to summary statistics at each visit.
Baseline value is the last value taken prior to study drug administration.
Change from baseline includes only those subjects with both a baseline value and a value for then summarized time period.

Cross Reference: Listing 16.2.9

Table 14.3.4.5 Summary of Vital Signs
Respiration Rate (breaths/min)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cohort 3	Day 7-20hr Post	2	39.5	13.44	39.5	30	49	2	-7.5	9.19	-7.5	-14	-1
	Day 7-24hr Post	2	46.0	11.31	46.0	38	54	2	-1.0	7.07	-1.0	-6	4
	Day 11	2	44.5	7.78	44.5	39	50	2	-2.5	12.02	-2.5	-11	6
	Day 11-Pre-dose	2	44.5	7.78	44.5	39	50	2	-2.5	12.02	-2.5	-11	6
	Day 11-15min Post	2	35.0	4.24	35.0	32	38	2	-12.0	0.00	-12.0	-12	-12
	Day 11-1hr Post	2	33.5	7.78	33.5	28	39	2	-13.5	12.02	-13.5	-22	-5
	Day 11-4hr Post	2	32.0	5.66	32.0	28	36	2	-15.0	1.41	-15.0	-16	-14
	Day 11-8hr Post	2	36.5	6.36	36.5	32	41	2	-10.5	2.12	-10.5	-12	-9
	Day 11-12hr Post	2	35.0	15.56	35.0	24	46	2	-12.0	19.80	-12.0	-26	2
	Day 11-16hr Post	2	37.0	12.73	37.0	28	46	2	-10.0	16.97	-10.0	-22	2
	Day 11-20hr Post	2	40.0	5.66	40.0	36	44	2	-7.0	9.90	-7.0	-14	0
	Day 11-24hr Post	2	41.0	1.41	41.0	40	42	2	-6.0	5.66	-6.0	-10	-2
	Day 14	2	44.0	5.66	44.0	40	48	2	-3.0	9.90	-3.0	-10	4
	Day 14-Pre-dose	2	44.0	5.66	44.0	40	48	2	-3.0	9.90	-3.0	-10	4
	Day 14-15min Post	2	46.0	8.49	46.0	40	52	2	-1.0	12.73	-1.0	-10	8
	Day 14-1hr Post	1	29.0		29.0	29	29	1	-15.0		-15.0	-15	-15
	Day 14-4hr Post	2	39.0	7.07	39.0	34	44	2	-8.0	2.83	-8.0	-10	-6
	Day 14-8hr Post	2	44.5	10.61	44.5	37	52	2	-2.5	6.36	-2.5	-7	2
	Day 14-12hr Post	2	52.5	6.36	52.5	48	57	2	5.5	10.61	5.5	-2	13
	Day 14-16hr Post	2	49.5	9.19	49.5	43	56	2	2.5	13.44	2.5	-7	12
	Day 14-20hr Post	2	37.0	9.90	37.0	30	44	2	-10.0	5.66	-10.0	-14	-6
	Day 14-24hr Post	2	38.0	2.83	38.0	36	40	2	-9.0	7.07	-9.0	-14	-4
	Day 15	2	52.0	5.66	52.0	48	56	2	5.0	9.90	5.0	-2	12
	Day 21	2	43.5	12.02	43.5	35	52	2	-3.5	16.26	-3.5	-15	8
	Month 2	2	59.0	7.07	59.0	54	64	2	12.0	2.83	12.0	10	14
	Month 4	2	38.0	2.83	38.0	36	40	2	-9.0	1.41	-9.0	-10	-8
	Month 6	2	27.0	1.41	27.0	26	28	2	-20.0	5.66	-20.0	-24	-16
Overall	Baseline	10	46.7	8.38	44.5	33	61						
	Day 0	10	39.7	8.12	42.0	25	50	10	-7.0	8.65	-8.0	-20	9
	Day 0-Pre-dose	10	37.1	6.72	40.5	25	44	10	-9.6	6.72	-8.5	-20	0
	Day 0-15min Post	10	44.2	9.37	45.0	30	60	10	-2.5	12.20	-2.0	-23	16
	Day 0-1hr Post	10	42.4	10.23	41.5	31	64	10	-4.3	15.21	-4.5	-30	22
	Day 0-4hr Post	10	43.7	7.67	44.5	29	57	10	-3.0	9.14	-3.0	-16	11

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Cross Reference: Listing 16.2.9

Table 14.3.4.5 Summary of Vital Signs
Respiration Rate (breaths/min)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Overall	Day 0-8hr Post	9	41.0	8.08	37.0	34	60	9	-5.3	11.92	-3.0	-24	10
	Day 0-12hr Post	10	39.6	7.35	38.5	30	52	10	-7.1	10.29	-8.0	-18	19
	Day 0-16hr Post	10	45.7	7.29	43.0	38	59	10	-1.0	10.89	-1.0	-23	16
	Day 0-20hr Post	10	44.7	12.39	42.0	24	61	10	-2.0	12.57	-1.5	-21	18
	Day 0-24hr Post	2	39.0	4.24	39.0	36	42	2	-8.0	8.49	-8.0	-14	-2
	Day 1	10	43.4	10.04	42.0	24	59	10	-3.3	13.39	-4.0	-21	16
	Day 4	10	43.5	7.88	42.5	32	58	10	-3.2	9.93	-5.5	-15	13
	Day 4-Pre-dose	10	42.3	7.97	41.0	32	58	10	-4.4	9.88	-5.5	-20	8
	Day 4-15min Post	10	35.7	4.40	36.0	28	44	10	-11.0	9.24	-11.0	-24	5
	Day 4-1hr Post	10	37.1	7.48	35.0	28	48	10	-9.6	10.15	-9.5	-32	4
	Day 4-4hr Post	10	37.4	6.59	37.5	28	49	10	-9.3	9.07	-10.0	-26	5
	Day 4-8hr Post	10	39.9	7.22	40.5	27	50	10	-6.8	11.67	-6.5	-25	15
	Day 4-12hr Post	10	39.0	6.55	39.0	29	48	10	-7.7	9.42	-4.0	-27	5
	Day 4-16hr Post	9	40.4	6.37	43.0	31	48	9	-4.7	9.29	-2.0	-15	13
	Day 4-20hr Post	9	41.2	12.86	39.0	23	67	9	-3.9	15.10	-8.0	-22	24
	Day 4-24hr Post	2	39.0	4.24	39.0	36	42	2	-8.0	8.49	-8.0	-14	-2
	Day 7	10	46.3	6.88	45.5	37	57	10	-0.4	9.99	-1.0	-20	17
	Day 7-Pre-dose	10	44.9	7.96	43.5	36	57	10	-1.8	9.86	-3.5	-20	17
	Day 7-15min Post	10	45.9	7.49	46.5	36	58	10	-0.8	11.57	4.5	-22	9
	Day 7-1hr Post	10	43.3	10.57	41.0	31	59	10	-3.4	12.09	1.5	-30	11
	Day 7-4hr Post	10	44.1	9.46	44.0	31	62	10	-2.6	11.90	-1.0	-28	14
	Day 7-8hr Post	10	38.2	9.94	36.5	28	62	10	-8.5	13.84	-4.5	-28	12
	Day 7-12hr Post	10	41.1	8.32	42.0	27	52	10	-5.6	12.84	-6.0	-34	9
	Day 7-16hr Post	10	38.6	7.01	37.5	31	50	10	-8.1	12.06	-7.0	-26	12
	Day 7-20hr Post	10	42.6	8.25	41.5	30	54	10	-4.1	10.02	-0.5	-26	8
	Day 7-24hr Post	2	46.0	11.31	46.0	38	54	2	-1.0	7.07	-1.0	-6	4
	Day 11	10	44.1	5.51	43.0	37	51	10	-2.6	11.93	1.5	-24	8
	Day 11-Pre-dose	10	45.7	6.33	46.0	38	56	10	-1.0	12.28	5.5	-22	11
	Day 11-15min Post	10	41.0	7.23	39.5	32	54	10	-5.7	9.33	-6.0	-23	9
	Day 11-1hr Post	10	40.1	9.75	39.5	28	59	10	-6.6	12.12	-4.5	-25	16
	Day 11-4hr Post	10	41.3	7.80	40.0	28	54	10	-5.4	11.66	-5.5	-21	21
	Day 11-8hr Post	10	39.2	6.21	40.5	29	47	10	-7.5	11.63	-6.5	-32	8
	Day 11-12hr Post	10	36.1	10.94	36.0	23	58	10	-10.6	13.18	-3.5	-35	2
	Day 11-16hr Post	9	40.4	9.58	38.0	28	57	9	-7.1	16.85	-7.0	-32	24

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Change from baseline includes only those subjects with both a baseline value and a value for then summarized time period.

Cross Reference: Listing 16.2.9

Table 14.3.4.5 Summary of Vital Signs
Respiration Rate (breaths/min)

		Actual Values						Change From Baseline					
Treatment	Scheduled Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Overall	Day 11-20hr Post	9	41.3	8.17	42.0	29	53	9	-6.2	12.99	-2.0	-32	8
	Day 11-24hr Post	2	41.0	1.41	41.0	40	42	2	-6.0	5.66	-6.0	-10	-2
	Day 14	10	41.5	4.03	41.0	34	48	10	-5.2	10.42	-5.0	-23	11
	Day 14-Pre-dose	10	42.5	4.50	43.0	34	48	10	-4.2	11.23	-4.0	-23	11
	Day 14-15min Post	10	43.3	9.06	42.0	32	62	10	-3.4	13.78	0.0	-29	12
	Day 14-1hr Post	9	44.2	12.96	47.0	29	66	9	-2.1	16.97	3.0	-31	20
	Day 14-4hr Post	10	41.4	6.19	40.5	34	55	10	-5.3	11.75	-5.5	-24	22
	Day 14-8hr Post	10	45.4	12.62	45.0	28	67	10	-1.3	13.94	3.0	-22	18
	Day 14-12hr Post	10	41.8	8.20	40.0	30	57	10	-4.9	13.79	-3.5	-31	13
	Day 14-16hr Post	10	40.5	8.49	41.5	30	56	10	-6.2	14.76	-3.5	-29	13
	Day 14-20hr Post	10	40.1	6.92	41.5	29	48	10	-6.6	11.29	-8.0	-27	12
	Day 14-24hr Post	2	38.0	2.83	38.0	36	40	2	-9.0	7.07	-9.0	-14	-4
	Day 15	10	44.1	9.49	48.0	30	56	10	-2.6	16.53	1.5	-30	22
	Day 21	10	41.6	6.59	40.0	33	52	10	-5.1	11.18	-5.5	-24	8
	Month 2	10	40.5	12.72	37.0	24	64	10	-6.2	15.35	-10.5	-24	15
	Month 4	9	37.6	8.59	40.0	24	50	9	-7.6	12.03	-8.0	-26	7
	Month 6	10	33.0	8.33	30.5	22	48	10	-13.7	7.80	-13.5	-24	-1
Siblings	Enrollment	4	27.8	2.06	28.0	25	30						

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Baseline value is the last value taken prior to study drug administration.
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Cross Reference: Listing 16.2.9