Clinical trial results:
A trial of antigen-specific immune tolerance induction in mucopolysaccharidosis I (MPS I) patients initiating enzyme replacement therapy with Aldurazyme® (laronidase)

Summary

EudraCT number	2007-001163-30
Trial protocol	Outside EU/EEA
Global end of trial date	17 September 2012

Results information

Result version number	v1
This version publication date	22 June 2016
First version publication date	08 July 2015

Trial information

Trial identification

Sponsor protocol code	ALID02307

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00741338
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Genzyme Corporation
Sponsor organisation address	500 Kendall Street, Cambridge, MA, United States, 02142
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 August 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 September 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the antibody response to Aldurazyme in newly treated severe MPS I subjects following an antigen-specific immunosuppressive regimen.

Protection of trial subjects:

Pediatric Trial:
The study was conducted by investigators experienced in the treatment of pediatric subjects. The parent(s) or guardian(s) as well as the children were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in child-appropriate language was provided and explained to the child. Repeated invasive procedures were minimized. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anesthesia may have been used to minimize distress and discomfort.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	15 September 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Russian Federation: 3
Country: Number of subjects enrolled	Brazil: 3
Worldwide total number of subjects	6
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	1
Children (2-11 years)	5

Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 2 centers in Brazil and Russia between September 2008 and September 2013.

Pre-assignment

Screening details:

A total of 7 subjects were enrolled, 3 in Cohort 1 and 4 in Cohort 2. Of the 4 subjects enrolled in Cohort 2, one subject was screen failure.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1

Arm description:

Tolerance Induction Period (TIP): Cyclosporine A (CsA) starting at 5 milligram per kilogram (mg/kg) orally three times daily until the target trough concentration of at least 350 nanogram per milliliter (ng/mL) (preferably 400 ng/mL) achieved along with azathioprine (Aza) 2.5 mg/kg/day orally. Once target CsA trough level achieved and maintained for at least 1 week, subjects received laronidase 0.058 mg/kg (low-dose) once weekly intravenous (IV) infusion (starting from Day 1) up to Week 12. CsA and Aza were gradually discontinued. Immune Challenge Period (ICP): following TIP, laronidase dose increased to 0.12 mg/kg once weekly IV infusion for 1 week followed by 0.25 mg/kg once weekly IV infusion for 1 week and then 0.58 mg/kg (full-dose) once weekly IV infusion up to Week 39.

Arm type	Experimental
Investigational medicinal product name	Laronidase
Investigational medicinal product code	
Other name	Aldurazyme®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

0.12 mg/kg once weekly IV infusion for 1 week followed by 0.25 mg/kg once weekly IV infusion for 1 week and then 0.58 mg/kg (full-dose) once weekly IV infusion up to Week 39.

Investigational medicinal product name	Cyclosporine
Investigational medicinal product code	
Other name	Neoral®
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

5 (mg/kg) orally three times daily until the target trough concentration of at least 350 nanogram per milliliter (ng/mL) (preferably 400 ng/mL) achieved along with azathioprine (Aza) 2.5 mg/kg/day orally. When targeted CsA level is achieved than dose of CsA and Aza were gradually discontinued.

Investigational medicinal product name	Azathioprine
Investigational medicinal product code	
Other name	Imuran®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2.5 mg/kg/day than gradually discontinued.

Arm title	Cohort 2

Arm description:

TIP: CsA starting at 6.7 mg/kg orally three times daily until the target trough concentration of at least 350 ng/mL (preferably 400 ng/mL) achieved along with Aza 5 mg/kg orally every other day. Once target CsA trough level achieved and maintained for at least 1 week, subjects received laronidase 0.058 mg/kg (low-dose) once weekly IV infusion (starting from Day 1) up to Week 18. CsA and Aza were gradually discontinued. ICP: following TIP, laronidase dose increased to 0.12 mg/kg once weekly IV infusion for 1 week followed by 0.25 mg/kg once weekly IV infusion for 1 week and then 0.58 mg/kg (full-dose) once weekly IV infusion up to Week 45.

Arm type	Experimental
Investigational medicinal product name	Laronidase
Investigational medicinal product code	
Other name	Aldurazyme®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Subjects received 0.058 mg/kg (low-dose) once weekly IV infusion (starting from Day 1) up to Week 18. Dose increased to 0.12 mg/kg once weekly IV infusion for 1 week followed by 0.25 mg/kg once weekly IV infusion for 1 week and then 0.58 mg/kg (full-dose) once weekly IV infusion up to Week 45.

Investigational medicinal product name	Cyclosporine
Investigational medicinal product code	
Other name	Neoral®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

6.7 mg/kg orally three times daily along with Aza every other day.

Investigational medicinal product name	Azathioprine
Investigational medicinal product code	
Other name	Imuran®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5 mg/kg orally every other day.

Number of subjects in period 1	Cohort 1	Cohort 2
Started	3	3
Completed	3	2
Not completed	0	1
'Adverse Event '	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1

Reporting group description:

Tolerance Induction Period (TIP): Cyclosporine A (CsA) starting at 5 milligram per kilogram (mg/kg) orally three times daily until the target trough concentration of at least 350 nanogram per milliliter (ng/mL) (preferably 400 ng/mL) achieved along with azathioprine (Aza) 2.5 mg/kg/day orally. Once target CsA trough level achieved and maintained for at least 1 week, subjects received laronidase 0.058 mg/kg (low-dose) once weekly intravenous (IV) infusion (starting from Day 1) up to Week 12. CsA and Aza were gradually discontinued. Immune Challenge Period (ICP): following TIP, laronidase dose increased to 0.12 mg/kg once weekly IV infusion for 1 week followed by 0.25 mg/kg once weekly IV infusion for 1 week and then 0.58 mg/kg (full-dose) once weekly IV infusion up to Week 39.

Reporting group title	Cohort 2

Reporting group description:

TIP: CsA starting at 6.7 mg/kg orally three times daily until the target trough concentration of at least 350 ng/mL (preferably 400 ng/mL) achieved along with Aza 5 mg/kg orally every other day. Once target CsA trough level achieved and maintained for at least 1 week, subjects received laronidase 0.058 mg/kg (low-dose) once weekly IV infusion (starting from Day 1) up to Week 18. CsA and Aza were gradually discontinued. ICP: following TIP, laronidase dose increased to 0.12 mg/kg once weekly IV infusion for 1 week followed by 0.25 mg/kg once weekly IV infusion for 1 week and then 0.58 mg/kg (full-dose) once weekly IV infusion up to Week 45.

Reporting group values	Cohort 1	Cohort 2	Total
Number of subjects	3	3	6
Age categorical Units: Subjects			

Age continuous			
The number of subjects for cohort 2 = 4. Data included 1 subject who was screen failure.			
Units: years			
arithmetic mean	2.6	3.77	
full range (min-max)	1.8 to 3.5	3 to 4.2	-
Gender categorical Units: Subjects			
Female	2	0	2
Male	1	3	4

End points

End points reporting groups

Reporting group title	Cohort 1

Reporting group description:

Tolerance Induction Period (TIP): Cyclosporine A (CsA) starting at 5 milligram per kilogram (mg/kg) orally three times daily until the target trough concentration of at least 350 nanogram per milliliter (ng/mL) (preferably 400 ng/mL) achieved along with azathioprine (Aza) 2.5 mg/kg/day orally. Once target CsA trough level achieved and maintained for at least 1 week, subjects received laronidase 0.058 mg/kg (low-dose) once weekly intravenous (IV) infusion (starting from Day 1) up to Week 12. CsA and Aza were gradually discontinued. Immune Challenge Period (ICP): following TIP, laronidase dose increased to 0.12 mg/kg once weekly IV infusion for 1 week followed by 0.25 mg/kg once weekly IV infusion for 1 week and then 0.58 mg/kg (full-dose) once weekly IV infusion up to Week 39.

Reporting group title	Cohort 2

Reporting group description:

TIP: CsA starting at 6.7 mg/kg orally three times daily until the target trough concentration of at least 350 ng/mL (preferably 400 ng/mL) achieved along with Aza 5 mg/kg orally every other day. Once target CsA trough level achieved and maintained for at least 1 week, subjects received laronidase 0.058 mg/kg (low-dose) once weekly IV infusion (starting from Day 1) up to Week 18. CsA and Aza were gradually discontinued. ICP: following TIP, laronidase dose increased to 0.12 mg/kg once weekly IV infusion for 1 week followed by 0.25 mg/kg once weekly IV infusion for 1 week and then 0.58 mg/kg (full-dose) once weekly IV infusion up to Week 45.

Primary: Number of Subjects Who Achieved Immune Tolerance Induction

End point title	Number of Subjects Who Achieved Immune Tolerance Induction[1]

End point description:

Immune tolerance induction success was defined as development of an anti-laronidase immunoglobulin G (IgG) antibody titer less than or equal to (<=) 1:3200 after 24 weeks of receiving full-dose (0.58 mg/kg) laronidase therapy. Safety population included all subjects who received any study drug treatment.

End point type	Primary

End point timeframe:

24 weeks after start of full-dose laronidase therapy

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for this outcome measure.

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	3		
Units: subjects	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Reduction of Urinary Glycosaminoglycan (uGAG) Level From Baseline to the End of Treatment/Early Withdrawal

End point title	Percent Reduction of Urinary Glycosaminoglycan (uGAG) Level From Baseline to the End of Treatment/Early Withdrawal

End point description:

Urinary Glycosaminoglycan (uGAG) Levels: concentration of glycosaminoglycan (GAG) relative to creatinine in urine. A greater decrease in uGAG level indicates a greater response. Safety population included all subjects who received any study drug treatment.

End point type	Secondary

End point timeframe:

Baseline, end of treatment/early withdrawal (up to 24 weeks after start of full-dose laronidase therapy)

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	3		
Units: subjects				
median (full range (min-max))	-43.8 (-61.7 to -6.7)	-72.5 (-84.2 to -62.5)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signature of informed consent up to 30 days after end of treatment/early withdrawal (end of treatment/early withdrawal: up to 24 weeks after start of full-dose laronidase therapy).

Adverse event reporting additional description:

Analysis was performed on safety population. In the event a single subject has experienced both a serious and a non-serious form of the same adverse event term, the subject has been included in the numerator ("number of affected subjects") of both adverse event tables.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Cohort 1

Reporting group description:

Tolerance Induction Period (TIP): Cyclosporine A (CsA) starting at 5 milligram per kilogram (mg/kg) orally three times daily until the target trough concentration of at least 350 nanogram per milliliter (ng/mL) (preferably 400 ng/mL) achieved along with azathioprine (Aza) 2.5 mg/kg/day orally. Once target CsA trough level achieved and maintained for at least 1 week, subjects received laronidase 0.058 mg/kg (low-dose) once weekly intravenous (IV) infusion (starting from Day 1) up to Week 12. CsA and Aza were gradually discontinued. Immune Challenge Period (ICP): following TIP, laronidase dose increased to 0.12 mg/kg once weekly IV infusion for 1 week followed by 0.25 mg/kg once weekly IV infusion for 1 week and then 0.58 mg/kg (full-dose) once weekly IV infusion up to Week 39.

Reporting group title	Cohort 2

Reporting group description:

TIP: CsA starting at 6.7 mg/kg orally three times daily until the target trough concentration of at least 350 ng/mL (preferably 400 ng/mL) achieved along with Aza 5 mg/kg orally every other day. Once target CsA trough level achieved and maintained for at least 1 week, subjects received laronidase 0.058 mg/kg (low- dose) once weekly IV infusion (starting from Day 1) up to Week 18. CsA and Aza were gradually discontinued. ICP: following TIP, laronidase dose increased to 0.12 mg/kg once weekly IV infusion for 1 week followed by 0.25 mg/kg once weekly IV infusion for 1 week and then 0.58 mg/kg (full-dose) once weekly IV infusion up to Week 45.

Serious adverse events	Cohort 1	Cohort 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 3 (66.67%)	1 / 3 (33.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			

subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device Related Infection			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Tract Infection Viral			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Cohort 1	Cohort 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	3 / 3 (100.00%)	
Vascular disorders			
Hyperaemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Hyperthermia			

subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Influenza Like Illness			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Medical Device Complication			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	
occurrences (all)	8	0	
Immune system disorders			
Drug Hypersensitivity			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	
occurrences (all)	4	0	
Rhinorrhoea			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Stridor			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Investigations			
Blood Pressure Increased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 3 (66.67%)	
occurrences (all)	0	2	

Head Circumference Abnormal			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Red Blood Cell Sedimentation Rate Increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Weight Decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Arthropod Sting			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Head Injury			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	2	
Iron Deficiency Anaemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Lymphocytosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Neutropenia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	
occurrences (all)	1	2	
Thrombocytosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	2	

Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	
occurrences (all)	8	0	
Diarrhoea			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	
occurrences (all)	2	1	
Gingival Cyst			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Flatulence			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Gingival Hyperplasia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Umbilical Hernia, Obstructive			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Dermatitis Allergic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Dermatitis Atopic			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Erythema			

subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Hand Dermatitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Heat Rash			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Hypertrichosis			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Ingrowing Nail			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	
occurrences (all)	3	0	
Papule			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Prurigo			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	2	
Rash			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Rash Papular			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Skin Maceration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	2	
Urticaria			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	
occurrences (all)	1	2	
Infections and infestations			

Ear Infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Folliculitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Giardiasis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Gingivitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Impetigo			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Laryngitis Viral			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Nematodiasis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Periodontitis			
subjects affected / exposed	0 / 3 (0.00%)	2 / 3 (66.67%)	
occurrences (all)	0	3	
Rash Pustular			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Respiratory Tract Infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Respiratory Tract Infection Viral			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	

Sinusitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Upper Respiratory Tract Infection			
subjects affected / exposed	3 / 3 (100.00%)	0 / 3 (0.00%)	
occurrences (all)	7	0	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 October 2007	-Added information on Ora-Blend® and provided instructions for creation of an oral liquid formulation of azathioprine by reconstitution of the tablet with Ora-Blend.
12 June 2008	-Increased the CsA dose in order to reach the target subject plasma level of CsA. - Modified the withdrawal rule regarding intravenous infusion antibiotics in recognition that intravenous infusion antibiotics are the treatment of choice in some countries. Thus, the modified rule bases withdrawal not on the type of treatment for an infection (oral versus intravenous) but rather on whether the infection is suspected to be due to the immunosuppressive therapy. - Added information pertaining to labeling, preparation, and storage of investigational products. - Clarified that the types of vaccines and the timing of vaccinations must comply with regional public health requirements. - Modified Inclusion Criterion #2 that the subjects' parents or legal guardian must be willing and able to comply with the trial procedures. - Added testing for immunization antibodies in order to determine whether booster shots are necessary for subjects. • Specified that measurement of vital signs may be clinically indicated and captured accordingly even if no abnormalities of the vital signs are assessed as infusion-associated reactions. • Specified that immunology testing should not be limited to just testing for medically important events assessed as hypersensitivity reactions because subjects who experience moderate or recurrent reactions (suspected not to represent a hypersensitivity reaction) may become immunoglobulin E positive and subject-specific infusion management and additional immunology testing may be warranted. • Clarified follow-up for adverse event reporting and specified that uncontrolled hypertension is to be reported as a SAE. • Added a review of safety data for Cohort 1 by an independent Data Monitoring Committee before commencement of dosing in Cohort 2. • Updated the schedule of assessments table to reflect the aforementioned changes.
10 February 2009	- Specified the use of a local laboratory for the analysis of hematology parameters to provide timely safety information to the Investigator. - Specified the use of a local laboratory for analysis of CsA trough levels to provide timely trough level information to the Investigator. - Clarified that a positive CsA trough level report from the central laboratory was necessary to begin low-dose Aldurazyme infusions. The local laboratory must report that the target level was reached in a sample taken approximately 1 week after the sample tested by the central laboratory. - Added a statement that subjects are to be encouraged to enroll in the MPS I Registry after completing the study.

11 December 2009	Details of the new immunosuppressive regimen was added for Cohort 2 : - Extension of the initial dosing period (for both CsA and azathioprine) from 4 weeks to 6 weeks in the Tolerance Induction Period. - Extension of the immunosuppressant step-down period from 4 weeks to 8 weeks, and number of Aldurazyme infusions increased by 6 (i.e., one infusion per each week). - Study duration of 6 weeks was increased. - Full dose of azathioprine was increased from 2.5 mg/kg to 5.0 mg/kg, and the dosing frequency was decreased from every day to every other day. specification that its administration is to be 3 oral doses given at 8-hour intervals. - Added text regarding the 30-day follow-up phone call in the protocol body and the schedule of events, clarified text regarding the use of subjects diary cards for collection of data on immunosuppressant usage, and made consistent the entry criteria contained in the synopsis with that in the body of the document. - Modified Exclusion Criterion #9 to state that subjects with a history of tuberculosis or a positive test for latent tuberculosis will be excluded from the study. - Modified Inclusion Criterion #6 to require that subjects had a documented α-L-iduronidase deficiency based on a fibroblast, plasma, serum, leukocyte, or dried blood spot α-L-iduronidase enzyme activity assay (not a level of ≤10% of the normal mean value of the measuring laboratory). - Added new Exclusion Criterion #3 to prevent enrollment of subjects with a severe hypersensitivity to any of the investigational drugs in the study. - Clarified that the "immune tolerance group" used for statistical comparisons is also called the "final cohort" or the "cohort that received the final regimen". - Corrected and clarified the roles of the Sponsor, Investigator, and Data Monitoring Committee. - Updated the definition of infusion-associated reaction to reflect the current definitions of the Sponsor's Global Pharmacovigilance & Epidemiology group.
08 May 2012	- Decreased the maximum number of cohorts from 3 to 2 due to difficulty in recruiting suitable subjects into the study. - Changed the success criteria of a cohort from 4 of 7 evaluable subjects to 3 of 7 evaluable subjects due to updated power calculations, and decreased the maximum number of subjects enrolled from 18 to 12. - Increased the upper age limit to include subjects who were 5 years of age at enrollment or younger. - Removed experimental immune assays as safety assessments for Cohort 2. - Clarified the processes for assessing infusion-associated reactions.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Study was discontinued on September 10,2013 due to changing standards of care for this population, practical infeasibility of routinely monitoring plasma CsA in clinical setting, inconclusive results of interim analysis and not due to safety concern.

Notes: