Clinical trial results:
A Controlled, Randomized, Two-arm, Open-label, Assessor-blinded, Multicenter Study of Intrathecal Idursulfase-IT Administered in Conjunction with ELAPRASE® in Pediatric Patients with Hunter Syndrome and Early Cognitive Impairment

Summary

EudraCT number	2013-002885-38
Trial protocol	GB ES FR
Global end of trial date	28 September 2017

Results information

Result version number	v1 (current)
This version publication date	13 April 2018
First version publication date	13 April 2018

Trial information

Trial identification

Sponsor protocol code	HGT-HIT-094

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02055118
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire Human Genetic Therapies, Inc
Sponsor organisation address	300 Shire Way, Lexington, MA, United States, 02421
Public contact	Study Physician, Shire, 1 866-842-5335, clinicaltransparency@shire.com
Scientific contact	Study Physician, Shire, 1 866-842-5335, clinicaltransparency@shire.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000294-PIP02-12
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	28 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 September 2017
Global end of trial reached?	Yes
Global end of trial date	28 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to determine the effect of the treatment regimen in pediatric subjects with Hunter syndrome and early cognitive impairment on the General Conceptual Ability (GCA) score as measured by the Differential Ability Scales, Second Edition (DAS-II), in conjunction with ELAPRASE therapy.

Protection of trial subjects:

The procedures set out in the study protocol, pertaining to the conduct, evaluation, and documentation of this study, were designed to ensure that the sponsor and investigators abided by GCP as described in 21 CFR Parts 50, 56, and 312 and the ICH GCP Guidelines. Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki and its revisions.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 March 2014
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	Australia: 1
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	United States: 32
Worldwide total number of subjects	49
EEA total number of subjects	10

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)	0
Children (2-11 years)	48
Adolescents (12-17 years)	1
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 9 centers in Australia, Canada, France, Mexico, Spain, the United Kingdom and the United States between 24 Mar 2014 (first subject first visit) and 28 Sep 2017 (last subject last visit).

Pre-assignment

Screening details:

Overall, 103 subjects were screened, of them 54 subjects failed to meet the randomization and remaining 49 subjects were randomized to receive either IT treatment or No IT treatment.

Period 1

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

Blinding implementation details:

The assessor was blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	No IT Treatment

Arm description:

Subjects aged 3 to less than (<) 18 years received elaprase therapy intravenously as standard of care for 12 months.

Arm type	Standard of Care
Investigational medicinal product name	Elaprase
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects aged 3 to < 18 years received elaprase therapy intravenously as standard of care for 12 months.

Arm title	IT Treatment

Arm description:

Subjects aged 3 to < 18 years received intrathecal (IT) injections of 10 milligram (mg) idursulfase-IT once monthly for 12 months through SOPH-A-PORT Mini S intrathecal drug delivery device (IDDD) along with elaprase therapy.

Arm type	Experimental
Investigational medicinal product name	Idursulfase
Investigational medicinal product code	SHP609, HGT-2310
Other name	Idursulfase-IT
Pharmaceutical forms	Solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

Subjects aged 3 to < 18 years received IT injections of 10 mg idursulfase-IT once monthly for 12 months through SOPH-A-PORT Mini S IDDD along with elaprase.

Investigational medicinal product name	Elaprase
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects aged 3 to < 18 years received elaprase therapy intravenously as standard of care for 12 months.

Number of subjects in period 1	No IT Treatment	IT Treatment
Started	15	34
Completed	15	32
Not completed	0	2
Consent withdrawn by subject	-	2

Baseline characteristics

Reporting groups	
Reporting group title	No IT Treatment
Reporting group description:	
Subjects aged 3 to less than (<) 18 years received elaprase therapy intravenously as standard of care for 12 months.	
Reporting group title	IT Treatment
Reporting group description:	
Subjects aged 3 to < 18 years received intrathecal (IT) injections of 10 milligram (mg) idursulfase-IT once monthly for 12 months through SOPH-A-PORT Mini S intrathecal drug delivery device (IDDD) along with elaprase therapy.	

Reporting group values	No IT Treatment	IT Treatment	Total
Number of subjects	15	34	49
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	5.29	4.95	
standard deviation	± 2.624	± 1.496	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	15	34	49
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	5	9	14
Not Hispanic or Latino	8	25	33
Unknown or Not Reported	2	0	2
Race/Ethnicity, Customized Units: Subjects			
Race Asian	0	4	4
Race Black or African American	0	1	1
Race White	12	23	35
Race Other	3	6	9

End points

End points reporting groups

Reporting group title	No IT Treatment
Reporting group description:	
Subjects aged 3 to less than (<) 18 years received elaprase therapy intravenously as standard of care for 12 months.	
Reporting group title	IT Treatment
Reporting group description:	
Subjects aged 3 to < 18 years received intrathecal (IT) injections of 10 milligram (mg) idursulfase-IT once monthly for 12 months through SOPH-A-PORT Mini S intrathecal drug delivery device (IDDD) along with elaprase therapy.	

Primary: Change From Baseline in Differential Ability Scales, Second Edition (DAS-II) General Conceptual Ability (GCA) Standard Score at Week 52

End point title	Change From Baseline in Differential Ability Scales, Second Edition (DAS-II) General Conceptual Ability (GCA) Standard Score at Week 52
End point description:	
The DAS-II was used to assess cognitive development in all randomized subjects. The GCA standard score of the DAS-II was used to obtain a general measure of cognitive ability. The GCA score represent a score (mean = 100 and standard deviation of 15) on which higher scores indicate a higher level of cognitive ability. A positive change value indicates improvement in cognitive ability. Intent to treat (ITT) population included all randomized subjects.	
End point type	Primary
End point timeframe:	
Baseline, Week 52	

End point values	No IT Treatment	IT Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	29		
Units: Score on a scale				
least squares mean (standard error)				
Score on a scale	-7.4 (± 4.22)	-4.4 (± 3.14)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
The Mixed model repeated measures included fixed categorical effects for treatment, visit week, treatment by visit week interaction, baseline GCA classification factor (less than or equal to [<=] 70 or >70), baseline age group (<6 years or >=6 years), treatment by baseline GCA classification factor interaction, treatment by baseline age group interaction, interaction between baseline GCA classification factor and baseline age group, genotype, and the baseline GCA score as a continuous covariate.	
Comparison groups	IT Treatment v No IT Treatment

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5669
Method	Mixed model repeated measures
Parameter estimate	Least squares mean
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.3
upper limit	13.3
Variability estimate	Standard error of the mean
Dispersion value	5.12

Secondary: Change From Baseline in the Vineland Adaptive Behavior Scales, Second Edition (VABS-II) Adaptive Behavior Composite (ABC) Score at Week 52

End point title	Change From Baseline in the Vineland Adaptive Behavior Scales, Second Edition (VABS-II) Adaptive Behavior Composite (ABC) Score at Week 52

End point description:

The VABS-II test measures adaptive behaviors, including the ability to cope with environmental changes, to learn new everyday skills, and to demonstrate independence. This test measures the following 5 key domains: communication, daily living skills, socialization, motor skills, and the adaptive behavior composite (a composite of the other 4 domains). The ABC ranges from 20 to 160 on which higher scores indicate a higher level of adaptive functioning. A positive change value indicates improvement in adaptive functioning. ITT population included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	No IT Treatment	IT Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	31		
Units: Score on a scale				
least squares mean (standard error)				
Score on a scale	-5.3 (± 2.55)	-5.0 (± 2.05)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The Mixed model repeated measures included fixed categorical effects for treatment, visit week, treatment by visit week interaction, baseline GCA classification factor (<= 70 or >70), baseline age group (<6 years or >=6 years), treatment by baseline GCA classification factor interaction, treatment by baseline age group interaction, interaction between baseline GCA classification factor and baseline

age group, genotype, and the baseline ABC score as a continuous covariate.

Comparison groups	No IT Treatment v IT Treatment
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9218
Method	Mixed model repeated measures
Parameter estimate	Least squares mean
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	6.6
Variability estimate	Standard error of the mean
Dispersion value	3.11

Secondary: Change From Baseline in the Differential Ability Scales, Second Edition (DAS-II) General Conceptual Ability (GCA) Standard Score at Weeks 16, 28 and 40

End point title	Change From Baseline in the Differential Ability Scales, Second Edition (DAS-II) General Conceptual Ability (GCA) Standard Score at Weeks 16, 28 and 40

End point description:

The DAS-II was used to assess cognitive development in all randomized subjects. The GCA standard score of the DAS-II was used to obtain a general measure of cognitive ability. The GCA score represent a score (mean = 100 and standard deviation of 15) on which higher scores indicate a higher level of cognitive ability. A positive change value indicates improvement in cognitive ability. In the below table, "n" signifies subjects who were evaluable for the specified category, respectively. ITT population included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline, Week 16, Week 28 and Week 40

End point values	No IT Treatment	IT Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	34		
Units: Score on a scale				
least squares mean (standard error)				
Week 16 (n=14,30)	-2.9 (± 3.33)	-0.6 (± 2.54)		
Week 28 (n=12,30)	-6.1 (± 3.34)	-0.3 (± 2.56)		
Week 40 (n=15,30)	-6.4 (± 3.87)	-3.2 (± 2.92)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Vineland Adaptive Behavior Scales, Second Edition (VABS-II) Adaptive Behavior Composite (ABC) Score at Weeks 16, 28 and 40

End point title	Change From Baseline in the Vineland Adaptive Behavior Scales, Second Edition (VABS-II) Adaptive Behavior Composite (ABC) Score at Weeks 16, 28 and 40

End point description:

The VABS-II test measures adaptive behaviors, including the ability to cope with environmental changes, to learn new everyday skills, and to demonstrate independence. This test measures the following 5 key domains: communication, daily living skills, socialization, motor skills, and the adaptive behavior composite (a composite of the other 4 domains). The ABC ranges from 20 to 160 on which higher scores indicate a higher level of adaptive functioning. A positive change value indicates improvement in adaptive functioning. In the below table, "n" signifies subjects who were evaluable for the specified category, respectively. ITT population included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline, Week 16, Week 28 and Week 40

End point values	No IT Treatment	IT Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	34		
Units: Score on a scale				
least squares mean (standard error)				
Week 16 (n=15,31)	-2.8 (± 2.21)	-3.1 (± 1.86)		
Week 28 (n=15,29)	-1.1 (± 2.45)	-1.8 (± 2.01)		
Week 40 (n=14,30)	-3.3 (± 2.41)	-4.7 (± 1.97)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Differential Ability Scales, Second Edition (DAS-II) Cluster Standard Scores at Weeks 16, 28, 40 and 52

End point title	Change From Baseline in Differential Ability Scales, Second Edition (DAS-II) Cluster Standard Scores at Weeks 16, 28, 40 and 52

End point description:

The DAS-II was used to assess cognitive development in all randomized subjects. The cluster score represents a score (mean = 100 and standard deviation of 15) on which higher scores indicate a higher level of cognitive ability. In the below table, "n" signifies subjects who were evaluable for the specified category, respectively. ITT population included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline, Week 16, Week 28, Week 40 and Week 52

End point values	No IT Treatment	IT Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	34		
Units: Score on a scale				
least squares mean (standard error)				
Week 16: Verbal (n=15,32)	-1.1 (± 3.75)	-6.9 (± 2.81)		
Week 16: Nonverbal (n=14,32)	-6.7 (± 5.06)	2.6 (± 3.82)		
Week 16: Spatial (n=11,28)	-5.6 (± 3.18)	1.9 (± 2.47)		
Week 16: Special Nonverbal Composite (n=11,28)	-7.4 (± 3.95)	-0.7 (± 2.96)		
Week 28: Verbal (n=12,30)	-7.0 (± 4.26)	-5.1 (± 3.10)		
Week 28: Nonverbal (n=12,30)	-8.8 (± 5.41)	0.7 (± 4.06)		
Week 28: Spatial (n=9,27)	-7.8 (± 3.66)	-0.8 (± 2.70)		
Week 28: Special Nonverbal Composite) (n=9,27)	-8.0 (± 4.01)	-1.7 (± 3.00)		
Week 40: Verbal (n=15,30)	-7.3 (± 4.01)	-10.8 (± 3.07)		
Week 40: Nonverbal (n=15,30)	-8.7 (± 5.35)	-2.8 (± 4.09)		
Week 40: Spatial (n=11,27)	-7.3 (± 4.39)	0.6 (± 3.13)		
Week 40: Special Nonverbal Composite (n=11,27)	-9.7 (± 5.51)	-3.1 (± 3.78)		
Week 52: Verbal (n=15,30)	-5.7 (± 4.45)	-9.8 (± 3.31)		
Week 52: Nonverbal (n=15,30)	-11.2 (± 5.61)	-1.5 (± 4.25)		
Week 52: Spatial (n=11,26)	-9.6 (± 4.21)	-4.8 (± 3.04)		
Week 52: Special Nonverbal Composite (n=11,26)	-11.8 (± 5.38)	-5.0 (± 3.74)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Vineland Adaptive Behavior Scales, Second Edition (VABS-II) Standard Scores of Other Domains at Weeks 16, 28, 40, 52

End point title	Change From Baseline in Vineland Adaptive Behavior Scales, Second Edition (VABS-II) Standard Scores of Other Domains at Weeks 16, 28, 40, 52

End point description:

The VABS-II test measures adaptive behaviors, including the ability to cope with environmental changes, to learn new everyday skills, and to demonstrate independence. This test measures the following 5 key domains: communication, daily living skills, socialization, motor skills, and the adaptive behavior composite (a composite of the other 4 domains). The standard scores represent a score (mean = 100 and standard deviation of 15) on which higher scores indicate a higher level of cognitive ability. A positive change value indicates improvement in adaptive functioning. Communication, daily living skills, socialization and motor skills domains were reported here. In the below table, "n" signifies subjects who were evaluable for the specified category, respectively. ITT population included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline, Week 16, Week 28, Week 40, Week 52

End point values	No IT Treatment	IT Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	34		
Units: Score on a scale				
least squares mean (standard error)				
Week 16: Communication (n=15,33)	-2.8 (± 2.65)	-1.7 (± 1.94)		
Week 16: Daily Living Skills (n=15,33)	-3.5 (± 3.11)	-3.5 (± 2.33)		
Week 16: Socialization (n=15,32)	-4.0 (± 2.43)	-2.0 (± 2.05)		
Week 16: Motor Skills (n=12,27)	1.0 (± 2.00)	0.0 (± 1.46)		
Week 28: Communication (n=15,30)	-2.4 (± 2.80)	-0.3 (± 2.08)		
Week 28: Daily Living Skills (n=15,30)	0.1 (± 3.40)	-2.0 (± 2.53)		
Week 28: Socialization (n=15,30)	-0.8 (± 2.37)	-0.2 (± 2.02)		
Week 28: Motor Skills (n=12,25)	-0.2 (± 2.46)	0.7 (± 1.77)		
Week 40: Communication (n=14,32)	-3.5 (± 2.82)	-4.6 (± 2.07)		
Week 40: Daily Living Skills (n=15,31)	-2.0 (± 3.47)	-3.7 (± 2.57)		
Week 40: Socialization (n=15,32)	-4.0 (± 2.65)	-3.8 (± 2.17)		
Week 40: Motor Skills (n=12,26)	-2.2 (± 2.47)	-1.1 (± 1.77)		
Week 52: Communication (n=15,32)	-4.8 (± 2.99)	-5.8 (± 2.18)		
Week 52: Daily Living Skills (n=14,32)	-4.5 (± 3.50)	-4.4 (± 2.57)		
Week 52: Socialization (n=15,32)	-5.8 (± 2.72)	-2.8 (± 2.21)		
Week 52: Motor Skills (n=12,26)	-5.7 (± 2.47)	-1.3 (± 1.77)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Age Equivalents for Early Age of Core Subtests of the Differential Ability Scales, Second Edition (DAS-II) at Weeks 16, 28, 40 and 52

End point title	Change From Baseline of Age Equivalents for Early Age of Core Subtests of the Differential Ability Scales, Second Edition (DAS-II) at Weeks 16, 28, 40 and 52

End point description:

The DAS-II was used to assess cognitive development in all randomized subjects. The early years battery is designed for children ages 2 years 6 months through 6 years 11 months. The higher score indicates greater cognitive ability. The subtest score represent a score (mean = 50 and standard deviation of 10) on which higher scores indicate a higher level of cognitive ability. A positive change value indicates improvement in cognitive ability. In the below table, "n" signifies subjects who were evaluable for the specified category, respectively. ITT population who have been evaluated by the DAS-II test for early years were analysed.

End point type	Secondary

End point timeframe:

Baseline, Week 16, Week 28, Week 40 and Week 52

End point values	No IT Treatment	IT Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	32		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 16: Verbal Comprehension (n=14,29)	0.05 (± 0.748)	0.03 (± 0.700)		
Week 16: Picture Similarities (n=14,29)	0.00 (± 1.056)	0.48 (± 1.002)		
Week 16: Naming Vocabulary (n=14,29)	0.18 (± 0.432)	-0.02 (± 0.702)		
Week 16: Pattern Construction (n=14,27)	-0.14 (± 0.435)	0.25 (± 0.475)		
Week 16: Matrices (n=10,27)	0.48 (± 2.076)	0.38 (± 1.322)		
Week 16: Copying (n=10,27)	0.05 (± 0.197)	0.10 (± 0.211)		
Week 28: Verbal Comprehension (n=11,28)	-0.16 (± 0.846)	0.39 (± 0.780)		
Week 28: Picture Similarities (n=11,28)	0.39 (± 1.051)	0.43 (± 0.693)		
Week 28: Naming Vocabulary (n=11,28)	0.27 (± 0.325)	0.26 (± 0.870)		
Week 28: Pattern Construction (n=11,28)	-0.18 (± 0.389)	0.29 (± 0.543)		
Week 28: Matrices (n=8,25)	0.78 (± 1.089)	0.51 (± 1.802)		
Week 28: Copying (n=8,25)	0.06 (± 0.291)	0.14 (± 0.361)		
Week 40: Verbal Comprehension (n=14,27)	-0.11 (± 0.783)	0.17 (± 0.519)		
Week 40: Picture Similarities (n=14,27)	0.23 (± 1.277)	0.52 (± 1.081)		
Week 40: Naming Vocabulary (n=14,27)	-0.04 (± 0.950)	0.17 (± 0.721)		
Week 40: Pattern Construction (n=14,27)	-0.02 (± 0.317)	0.43 (± 0.733)		
Week 40: Matrices (n=10,24)	0.15 (± 1.890)	0.45 (± 1.721)		
Week 40: Copying (n=10,24)	0.33 (± 0.472)	0.30 (± 0.556)		
Week 52: Verbal Comprehension (n=14,27)	0.16 (± 1.090)	0.32 (± 0.657)		
Week 52: Picture Similarities (n=14,27)	0.27 (± 1.207)	0.84 (± 1.215)		
Week 52: Naming Vocabulary (n=14,27)	0.16 (± 0.959)	0.34 (± 1.006)		
Week 52: Pattern Construction (n=14,27)	0.02 (± 0.360)	0.31 (± 0.660)		
Week 52: Matrices (n=10,24)	0.00 (± 1.863)	0.64 (± 1.771)		
Week 52: Copying (n=10,23)	0.20 (± 0.438)	0.28 (± 0.502)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Age Equivalents for School Age of Core Subtests of the Differential Ability Scales, Second Edition (DAS-II) at Weeks 16, 28, 40 and 52

End point title	Change From Baseline of Age Equivalents for School Age of Core Subtests of the Differential Ability Scales, Second Edition (DAS-II) at Weeks 16, 28, 40 and 52

End point description:

The DAS-II was used to assess cognitive development in all randomized subjects. The school age battery is designed for children ages 7 years 0 months through 17 years 11 months. The higher score indicates greater cognitive ability. The subtest score represent a score (mean = 50 and standard deviation of 10) on which higher scores indicate a higher level of cognitive ability. A positive change value indicates improvement in cognitive ability. In the below table, "n" signifies subjects who were evaluable for the specified category, respectively and "99999" indicates that the standard deviation was not calculated due to less number of subjects. ITT population who have been evaluated by the DAS-II test for school age were analysed.

End point type	Secondary

End point timeframe:

Baseline, Week 16, Week 28, Week 40 and Week 52

End point values	No IT Treatment	IT Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	4		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 16: Recall of Designs (n=1,2)	-1.75 (± 99999)	1.00 (± 1.414)		
Week 16: Word Definitions (n=1,2)	1.50 (± 99999)	0.25 (± 0.707)		
Week 16: Pattern Construction (n=1,2)	1.00 (± 99999)	-0.13 (± 0.177)		
Week 16: Matrices (n=1,2)	-0.75 (± 99999)	0.38 (± 2.652)		
Week 16: Verbal Similarities (n=1,2)	0.75 (± 99999)	0.63 (± 0.884)		
Week 16: SQR (n=1,2)	1.17 (± 99999)	0.63 (± 0.884)		
Week 28: Recall of Designs (n=1,1)	-1.00 (± 99999)	0.00 (± 99999)		
Week 28: Word Definitions (n=1,1)	1.50 (± 99999)	-0.25 (± 99999)		
Week 28: Pattern Construction (n=1,1)	1.50 (± 99999)	-1.75 (± 99999)		
Week 28: Matrices (n=1,1)	-2.50 (± 99999)	0.00 (± 99999)		
Week 28: Verbal Similarities (n=1,1)	0.75 (± 99999)	0.00 (± 99999)		
Week 28: SQR (n=1,1)	0.25 (± 99999)	0.75 (± 99999)		
Week 40: Recall of Designs (n=1,1)	-2.00 (± 99999)	0.00 (± 99999)		
Week 40: Word Definitions (n=1,1)	1.50 (± 99999)	-0.25 (± 99999)		
Week 40: Pattern Construction (n=1,1)	1.92 (± 99999)	0.00 (± 99999)		
Week 40: Matrices (n=1,1)	-2.25 (± 99999)	1.25 (± 99999)		
Week 40: Verbal Similarities (n=1,1)	0.75 (± 99999)	1.00 (± 99999)		
Week 40: SQR (n=1,1)	1.17 (± 99999)	1.00 (± 99999)		
Week 52: Recall of Designs (n=1,1)	-2.50 (± 99999)	0.00 (± 99999)		
Week 52: Word Definitions (n=1,1)	1.75 (± 99999)	-0.25 (± 99999)		
Week 52: Pattern Construction (n=1,1)	1.92 (± 99999)	-2.75 (± 99999)		
Week 52: Matrices (n=1,1)	-0.25 (± 99999)	0.00 (± 99999)		
Week 52: Verbal Similarities (n=1,1)	1.17 (± 99999)	0.00 (± 99999)		

Week 52: SQR (n=1,1)	0.67 (± 99999)	1.00 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Development Quotients for Early Age of Core Subtests of the Differential Ability Scales, Second Edition (DAS-II) at Weeks 16, 28, 40 and 52

End point title	Change From Baseline of Development Quotients for Early Age of Core Subtests of the Differential Ability Scales, Second Edition (DAS-II) at Weeks 16, 28, 40 and 52

End point description:

The DAS-II was used to assess cognitive development in all randomized subjects. The early years battery is designed for children ages 2 years 6 months through 6 years 11 months. The higher score indicates greater cognitive ability. The subtest score represent a score (mean = 50 and standard deviation of 10) on which higher scores indicate a higher level of cognitive ability. A positive change value indicates improvement in cognitive ability. In the below table, "n" signifies subjects who were evaluable for the specified category, respectively. ITT population who have been evaluated by the DAS-II test for early years were analysed.

End point type	Secondary

End point timeframe:

Baseline, Week 16, Week 28, Week 40 and Week 52

End point values	No IT Treatment	IT Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	32		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 16: Verbal Comprehension (n=14,29)	-5.91 (± 13.454)	-4.71 (± 12.990)		
Week 16: Picture Similarities (n=14,29)	-4.91 (± 16.959)	3.41 (± 19.157)		
Week 16: Naming Vocabulary (n=14,29)	-2.09 (± 7.758)	-5.44 (± 11.221)		
Week 16: Pattern Construction (n=14,27)	-7.79 (± 7.339)	-0.43 (± 9.213)		
Week 16: Matrices (n=10,27)	4.60 (± 30.134)	0.57 (± 24.054)		
Week 16: Copying (n=10,27)	-4.59 (± 4.206)	-4.15 (± 4.794)		
Week 28: Verbal Comprehension (n=11,28)	-14.05 (± 16.558)	-1.46 (± 15.790)		
Week 28: Picture Similarities (n=11,28)	-1.89 (± 17.409)	0.03 (± 14.733)		
Week 28: Naming Vocabulary (n=11,28)	-3.78 (± 6.970)	-3.76 (± 18.235)		
Week 28: Pattern Construction (n=11,28)	-11.95 (± 7.039)	-3.09 (± 10.708)		

Week 28: Matrices (n=8,25)	2.96 (± 18.576)	0.45 (± 34.931)		
Week 28: Copying (n=8,25)	-6.88 (± 5.759)	-6.66 (± 7.820)		
Week 40: Verbal Comprehension (n=14,27)	-15.40 (± 17.544)	-8.97 (± 11.618)		
Week 40: Picture Similarities (n=14,27)	-6.86 (± 19.775)	-3.11 (± 20.029)		
Week 40: Naming Vocabulary (n=14,27)	-10.02 (± 13.307)	-8.96 (± 14.427)		
Week 40: Pattern Construction (n=14,27)	-11.56 (± 6.989)	-3.89 (± 13.394)		
Week 40: Matrices (n=10,24)	-7.79 (± 24.750)	-5.73 (± 32.283)		
Week 40: Copying (n=10,24)	-6.15 (± 9.533)	-7.69 (± 11.208)		
Week 52: Verbal Comprehension (n=14,27)	-14.49 (± 22.614)	-8.59 (± 13.473)		
Week 52: Picture Similarities (n=14,27)	-8.32 (± 19.393)	0.56 (± 22.325)		
Week 52: Naming Vocabulary (n=14,27)	-10.29 (± 13.522)	-8.20 (± 18.543)		
Week 52: Pattern Construction (n=14,27)	-13.59 (± 8.232)	-8.49 (± 11.528)		
Week 52: Matrices (n=10,24)	-12.47 (± 23.892)	-5.53 (± 32.584)		
Week 52: Copying (n=10,23)	-10.19 (± 9.608)	-10.34 (± 10.429)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Development Quotients for School Age of Core Subtests of the Differential Ability Scales, Second Edition (DAS-II) at Weeks 16, 28, 40 and 52

End point title	Change From Baseline of Development Quotients for School Age of Core Subtests of the Differential Ability Scales, Second Edition (DAS-II) at Weeks 16, 28, 40 and 52

End point description:

The DAS-II was used to assess cognitive development in all randomized subjects. The school age battery is designed for children ages 7 years 0 months through 17 years 11 months. The higher score indicates greater cognitive ability. The subtest score represent a score (mean = 50 and standard deviation of 10) on which higher scores indicate a higher level of cognitive ability. A positive change value indicates improvement in cognitive ability. In the below table, "n" signifies subjects who were evaluable for the specified category, respectively and "99999" indicates that the standard deviation was not calculated due to less number of subjects. ITT population who have been evaluated by the DAS-II test for school age were analysed.

End point type	Secondary

End point timeframe:

Baseline, Week 16, Week 28, Week 40 and Week 52

End point values	No IT Treatment	IT Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	4		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 16: Recall of Designs (n=1,2)	-15.10 (± 99999)	9.20 (± 17.395)		
Week 16: Word Definitions (n=1,2)	9.60 (± 99999)	0.00 (± 9.192)		
Week 16: Pattern Construction (n=1,2)	5.70 (± 99999)	-4.85 (± 2.051)		
Week 16: Matrices (n=1,2)	-7.60 (± 99999)	2.40 (± 33.800)		
Week 16: Verbal Similarities (n=1,2)	3.70 (± 99999)	4.65 (± 10.960)		
Week 16: SQR (n=1,2)	6.70 (± 99999)	4.50 (± 10.748)		
Week 28: Recall of Designs (n=1,1)	-10.40 (± 99999)	-4.80 (± 99999)		
Week 28: Word Definitions (n=1,1)	8.70 (± 99999)	-8.20 (± 99999)		
Week 28: Pattern Construction (n=1,1)	8.40 (± 99999)	-26.90 (± 99999)		
Week 28: Matrices (n=1,1)	-21.40 (± 99999)	-3.40 (± 99999)		
Week 28: Verbal Similarities (n=1,1)	2.60 (± 99999)	-4.80 (± 99999)		
Week 28: SQR (n=1,1)	-1.20 (± 99999)	4.40 (± 99999)		
Week 40: Recall of Designs (n=1,1)	-18.70 (± 99999)	-6.50 (± 99999)		
Week 40: Word Definitions (n=1,1)	7.50 (± 99999)	-9.90 (± 99999)		
Week 40: Pattern Construction (n=1,1)	10.20 (± 99999)	-7.20 (± 99999)		
Week 40: Matrices (n=1,1)	-20.50 (± 99999)	10.40 (± 99999)		
Week 40: Verbal Similarities (n=1,1)	1.40 (± 99999)	5.50 (± 99999)		
Week 40: SQR (n=1,1)	4.20 (± 99999)	5.50 (± 99999)		
Week 52: Recall of Designs (n=1,1)	-22.90 (± 99999)	-8.10 (± 99999)		
Week 52: Word Definitions (n=1,1)	8.40 (± 99999)	-11.50 (± 99999)		
Week 52: Pattern Construction (n=1,1)	9.20 (± 99999)	-41.00 (± 99999)		
Week 52: Matrices (n=1,1)	-6.90 (± 99999)	-5.70 (± 99999)		
Week 52: Verbal Similarities (n=1,1)	3.40 (± 99999)	-8.10 (± 99999)		
Week 52: SQR (n=1,1)	-0.40 (± 99999)	3.60 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of T-scores for Early Age of Core Subtests of the Differential Ability Scale, Second Edition (DAS-II) at Weeks 16, 28, 40 and 52

End point title	Change From Baseline of T-scores for Early Age of Core Subtests of the Differential Ability Scale, Second Edition (DAS-II) at Weeks 16, 28, 40 and 52

End point description:

The DAS-II was used to assess cognitive development in all randomized subjects. The early years battery is designed for children ages 2 years 6 months through 6 years 11 months. The higher score indicates greater cognitive ability. The subtest score represent a score (mean = 50 and standard deviation of 10) on which higher scores indicate a higher level of cognitive ability. A positive change value indicates improvement in cognitive ability. In the below table, "n" signifies subjects who were evaluable for the specified category, respectively. ITT population who have been evaluated by the DAS-II test for early years were analysed.

End point type	Secondary

End point timeframe:

Baseline, Week 16, Week 28, Week 40 and Week 52

End point values	No IT Treatment	IT Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	32		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 16: Verbal Comprehension (n=14,29)	-1.7 (± 7.27)	-3.6 (± 9.30)		
Week 16: Picture Similarities (n=14,29)	-2.3 (± 9.62)	2.1 (± 9.10)		
Week 16: Naming Vocabulary (n=14,29)	-0.1 (± 6.01)	-2.4 (± 6.21)		
Week 16: Pattern Construction (n=14,27)	-6.4 (± 6.01)	0.6 (± 8.77)		
Week 16: Matrices (n=10,27)	-4.3 (± 17.73)	0.4 (± 14.65)		
Week 16: Copying (n=10,27)	-2.2 (± 8.48)	-0.5 (± 8.76)		
Week 28: Verbal Comprehension (n=11,28)	-2.2 (± 10.32)	-1.8 (± 11.33)		
Week 28: Picture Similarities (n=11,28)	2.6 (± 7.97)	0.3 (± 6.28)		
Week 28: Naming Vocabulary (n=11,28)	-0.3 (± 4.13)	-2.0 (± 7.79)		
Week 28: Pattern Construction (n=11,28)	-8.9 (± 5.36)	-1.5 (± 9.74)		
Week 28: Matrices (n=8,25)	2.9 (± 6.47)	0.6 (± 16.09)		
Week 28: Copying (n=8,25)	-0.9 (± 6.36)	-1.6 (± 11.26)		
Week 40: Verbal Comprehension (n=14,27)	-4.9 (± 8.21)	-3.4 (± 6.55)		
Week 40: Picture Similarities (n=14,27)	0.1 (± 13.04)	-2.0 (± 9.81)		
Week 40: Naming Vocabulary (n=14,27)	-4.4 (± 9.69)	-3.9 (± 7.54)		
Week 40: Pattern Construction (n=14,27)	-8.7 (± 5.78)	-2.6 (± 11.24)		
Week 40: Matrices (n=10,24)	-7.4 (± 16.87)	-3.2 (± 16.71)		
Week 40: Copying (n=10,24)	-1.8 (± 11.39)	-0.1 (± 12.69)		
Week 52: Verbal Comprehension (n=14,27)	-4.6 (± 11.21)	-4.9 (± 11.10)		
Week 52: Picture Similarities (n=14,27)	-1.7 (± 15.41)	0.3 (± 10.44)		
Week 52: Naming Vocabulary (n=14,27)	-2.7 (± 8.59)	-3.2 (± 8.54)		

Week 52: Pattern Construction (n=14,27)	-10.9 (± 8.03)	-6.1 (± 10.90)		
Week 52: Matrices (n=10,24)	-8.5 (± 15.52)	-0.8 (± 17.00)		
Week 52: Copying (n=10,23)	-4.0 (± 10.68)	-2.4 (± 12.07)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of T-scores for School Age of Core Subtests of the Differential Ability Scale, Second Edition (DAS-II) at Weeks 16, 28, 40 and 52

End point title	Change From Baseline of T-scores for School Age of Core Subtests of the Differential Ability Scale, Second Edition (DAS-II) at Weeks 16, 28, 40 and 52

End point description:

The DAS-II was used to assess cognitive development in all randomized subjects. The school age battery is designed for children ages 7 years 0 months through 17 years 11 months. The higher score indicates greater cognitive ability. The subtest score represent a score (mean = 50 and standard deviation of 10) on which higher scores indicate a higher level of cognitive ability. A positive change value indicates improvement in cognitive ability. In the below table, "n" signifies subjects who were evaluable for the specified category, respectively and "99999" indicates that the standard deviation was not calculated due to less number of subjects. ITT population who have been evaluated by the DAS-II test for school age were analysed.

End point type	Secondary

End point timeframe:

Baseline, Week 16, Week 28, Week 40 and Week 52

End point values	No IT Treatment	IT Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	4		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 16: Recall of Designs (n=1,2)	-10.0 (± 99999)	5.0 (± 12.73)		
Week 16: Word Definitions (n=1,2)	7.0 (± 99999)	-0.5 (± 7.78)		
Week 16: Pattern Construction (n=1,2)	3.0 (± 99999)	-2.0 (± 1.41)		
Week 16: Matrices (n=1,2)	-5.0 (± 99999)	-0.5 (± 12.02)		
Week 16: Verbal Similarities (n=1,2)	4.0 (± 99999)	-4.0 (± 8.49)		
Week 16: SQR (n=1,2)	2.0 (± 99999)	3.0 (± 2.83)		
Week 28: Recall of Designs (n=1,1)	-7.0 (± 99999)	10.0 (± 99999)		
Week 28: Word Definitions (n=1,1)	5.0 (± 99999)	-8.0 (± 99999)		
Week 28: Pattern Construction (n=1,1)	4.0 (± 99999)	-19.0 (± 99999)		
Week 28: Matrices (n=1,1)	-12.0 (± 99999)	-9.0 (± 99999)		
Week 28: Verbal Similarities (n=1,1)	3.0 (± 99999)	-10.0 (± 99999)		
Week 28: SQR (n=1,1)	-2.0 (± 99999)	9.0 (± 99999)		
Week 40: Recall of Designs (n=1,1)	-14.0 (± 99999)	-4.0 (± 99999)		

Week 40: Word Definitions (n=1,1)	5.0 (± 99999)	-16.0 (± 99999)		
Week 40: Pattern Construction (n=1,1)	5.0 (± 99999)	-3.0 (± 99999)		
Week 40: Matrices (n=1,1)	-11.0 (± 99999)	1.0 (± 99999)		
Week 40: Verbal Similarities (n=1,1)	2.0 (± 99999)	1.0 (± 99999)		
Week 40: SQR (n=1,1)	1.0 (± 99999)	10.0 (± 99999)		
Week 52: Recall of Designs (n=1,1)	-17.0 (± 99999)	-4.0 (± 99999)		
Week 52: Word Definitions (n=1,1)	6.0 (± 99999)	-17.0 (± 99999)		
Week 52: Pattern Construction (n=1,1)	4.0 (± 99999)	-30.0 (± 99999)		
Week 52: Matrices (n=1,1)	-4.0 (± 99999)	-5.0 (± 99999)		
Week 52: Verbal Similarities (n=1,1)	5.0 (± 99999)	-10.0 (± 99999)		
Week 52: SQR (n=1,1)	-2.0 (± 99999)	9.0 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Age Equivalents Scores of Sub-domains of the Vineland Adaptive Behavior Scales, Second Edition (VABS-II) at Weeks 16, 28, 40 and 52

End point title	Change From Baseline of Age Equivalents Scores of Sub-domains of the Vineland Adaptive Behavior Scales, Second Edition (VABS-II) at Weeks 16, 28, 40 and 52

End point description:

The VABS-II test measures adaptive behaviors, including the ability to cope with environmental changes, to learn new everyday skills, and to demonstrate independence. The standard scores represent a score (mean = 100 and standard deviation of 15) on which higher scores indicate a higher level of cognitive ability. A positive change value indicates improvement in adaptive functioning. In the below table, "IR" indicates interpersonal relationship; "PLT" indicates play and leisure time and "DLS" indicates daily living skills. In the below table, "n" signifies subjects who were evaluable for the specified category, respectively. ITT population included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline, Week 16, Week 28, Week 40 and Week 52

End point values	No IT Treatment	IT Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	34		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 16: Communication- Expressive (n=15,33)	0.09 (± 0.512)	0.12 (± 0.544)		
Week 16: Communication- Receptive (n=15,33)	-0.09 (± 1.020)	-0.32 (± 1.845)		
Week 16: Communication- Written (n=15,33)	0.08 (± 0.406)	0.02 (± 0.572)		

Week 16: DLS- Community (n=15,33)	0.16 (± 0.583)	0.05 (± 0.710)		
Week 16: DLS- Domestic (n=15,33)	0.02 (± 1.477)	-0.09 (± 1.149)		
Week 16: DLS- Personal (n=15,33)	-0.23 (± 0.864)	-0.11 (± 0.599)		
Week 16: Socialization- Coping Skills (n=15,32)	-0.16 (± 0.712)	-0.09 (± 0.792)		
Week 16: Socialization- IR (n=15,33)	-0.09 (± 0.749)	0.04 (± 0.637)		
Week 16: Socialization- PLT (n=15,33)	0.21 (± 0.934)	0.11 (± 0.783)		
Week 16: Motor Skills- Fine (n=12,27)	0.30 (± 0.499)	0.29 (± 0.429)		
Week 16: Motor Skills- Gross (n=12,28)	0.17 (± 0.607)	0.36 (± 0.736)		
Week 28: Communication- Expressive (n=15,30)	0.28 (± 0.669)	0.36 (± 0.806)		
Week 28: Communication- Receptive (n=15,30)	0.83 (± 2.393)	0.44 (± 1.333)		
Week 28: Communication- Written (n=15,30)	0.21 (± 0.663)	0.18 (± 0.525)		
Week 28: DLS- Community (n=15,30)	0.22 (± 0.701)	0.26 (± 0.762)		
Week 28: DLS- Domestic (n=15,30)	0.67 (± 1.481)	0.34 (± 1.326)		
Week 28: DLS- Personal (n=15,30)	0.48 (± 1.260)	0.16 (± 0.544)		
Week 28: Socialization- Coping Skills (n=15,30)	0.29 (± 0.731)	0.27 (± 0.982)		
Week 28: Socialization- IR (n=15,30)	0.07 (± 0.884)	0.43 (± 0.876)		
Week 28: Socialization- PLT (n=15,30)	0.62 (± 0.818)	0.51 (± 1.017)		
Week 28: Motor Skills- Fine (n=12,25)	0.30 (± 0.403)	0.37 (± 0.533)		
Week 28: Motor Skills- Gross (n=12,26)	0.41 (± 0.588)	0.82 (± 1.061)		
Week 40: Communication- Expressive (n=15,32)	0.28 (± 0.679)	0.30 (± 0.764)		
Week 40: Communication- Receptive (n=15,32)	0.80 (± 2.388)	-0.07 (± 2.015)		
Week 40: Communication- Written (n=14,32)	0.30 (± 0.699)	0.00 (± 0.740)		
Week 40: DLS- Community (n=15,31)	0.38 (± 0.640)	0.02 (± 0.760)		
Week 40: DLS- Domestic (n=15,32)	0.72 (± 1.542)	0.39 (± 1.420)		
Week 40: DLS- Personal (n=15,32)	0.18 (± 0.720)	0.29 (± 0.587)		
Week 40: Socialization- Coping Skills (n=15,32)	0.14 (± 1.178)	0.26 (± 1.581)		
Week 40: Socialization- IR (n=15,32)	0.05 (± 0.796)	0.10 (± 0.973)		
Week 40: Socialization- PLT (n=15,32)	0.44 (± 0.808)	0.31 (± 0.921)		
Week 40: Motor Skills- Fine (n=12,26)	0.44 (± 0.453)	0.44 (± 0.640)		
Week 40: Motor Skills- Gross (n=12,27)	0.33 (± 0.662)	0.73 (± 0.990)		
Week 52: Communication- Expressive (n=15,32)	0.32 (± 0.973)	0.34 (± 0.858)		
Week 52: Communication- Receptive (n=15,32)	1.25 (± 2.253)	-0.05 (± 1.953)		
Week 52: Communication- Written (n=15,32)	0.16 (± 0.485)	0.11 (± 0.783)		
Week 52: DLS- Community (n=14,32)	0.36 (± 0.603)	0.30 (± 0.941)		
Week 52: DLS- Domestic (n=15,32)	0.27 (± 1.678)	0.37 (± 1.405)		
Week 52: DLS- Personal (n=15,32)	0.42 (± 0.572)	0.35 (± 0.840)		
Week 52: Socialization- Coping Skills (n=15,32)	0.29 (± 1.211)	0.31 (± 1.189)		
Week 52: Socialization- IR (n=15,32)	0.00 (± 0.752)	0.36 (± 1.005)		
Week 52: Socialization- PLT (n=15,32)	0.67 (± 1.446)	0.45 (± 0.839)		
Week 52: Motor Skills- Fine (n=12,26)	0.38 (± 0.365)	0.58 (± 0.645)		
Week 52: Motor Skills- Gross (n=12,27)	0.25 (± 0.773)	0.93 (± 1.008)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Development Quotients of Sub-domains of the Vineland Adaptive Behavior Scales, Second Edition (VABS-II) at Weeks 16, 28, 40 and 52

End point title	Change From Baseline of Development Quotients of Sub-domains of the Vineland Adaptive Behavior Scales, Second Edition (VABS-II) at Weeks 16, 28, 40 and 52

End point description:

The VABS-II test measures adaptive behaviors, including the ability to cope with environmental changes, to learn new everyday skills, and to demonstrate independence. The standard scores represent a score (mean = 100 and standard deviation of 15) on which higher scores indicate a higher level of cognitive ability. A positive change value indicates improvement in adaptive functioning. In the below table, "IR" indicates interpersonal relationship; "PLT" indicates play and leisure time and "DLS" indicates daily living skills. In the below table, "n" signifies subjects who were evaluable for the specified category, respectively. ITT population included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline, Week 16, Week 28, Week 40 and Week 52

End point values	No IT Treatment	IT Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	34		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 16: Communication- Expressive (n=15,33)	-1.09 (± 7.866)	-2.57 (± 11.781)		
Week 16: Communication- Receptive (n=15,33)	-2.58 (± 14.735)	-8.19 (± 26.774)		
Week 16: Communication- Written (n=15,33)	-4.10 (± 8.727)	-5.62 (± 12.554)		
Week 16: DLS- Community (n=15,33)	-0.37 (± 12.814)	-4.48 (± 15.498)		
Week 16: DLS- Domestic (n=15,33)	-2.80 (± 30.338)	-7.18 (± 24.610)		
Week 16: DLS- Personal (n=15,33)	-9.94 (± 21.052)	-6.35 (± 11.185)		
Week 16: Socialization- Coping Skills (n=15,32)	-9.08 (± 14.414)	-6.56 (± 15.923)		
Week 16: Socialization- IR (n=15,33)	-3.87 (± 9.602)	-3.17 (± 14.610)		
Week 16: Socialization- PLT (n=15,33)	1.66 (± 18.903)	-0.64 (± 15.366)		
Week 16: Motor Skills- Fine (n=12,27)	0.48 (± 12.969)	0.00 (± 10.308)		

Week 16: Motor Skills- Gross (n=12,28)	-3.92 (± 15.524)	1.28 (± 15.410)		
Week 28: Communication- Expressive (n=15,30)	-0.23 (± 11.301)	-0.59 (± 14.480)		
Week 28: Communication- Receptive (n=15,30)	3.30 (± 24.423)	0.50 (± 17.058)		
Week 28: Communication- Written (n=15,30)	-5.15 (± 13.510)	-6.54 (± 11.339)		
Week 28: DLS- Community (n=15,30)	-3.07 (± 13.984)	-2.80 (± 15.937)		
Week 28: DLS- Domestic (n=15,30)	6.75 (± 28.703)	-3.37 (± 25.635)		
Week 28: DLS- Personal (n=15,30)	3.41 (± 26.699)	-4.27 (± 12.124)		
Week 28: Socialization- Coping Skills (n=15,30)	-4.88 (± 15.881)	-2.45 (± 19.142)		
Week 28: Socialization- IR (n=15,30)	-2.30 (± 13.889)	2.16 (± 17.844)		
Week 28: Socialization- PLT (n=15,30)	8.17 (± 17.767)	4.49 (± 20.413)		
Week 28: Motor Skills- Fine (n=12,25)	-2.86 (± 9.014)	-2.05 (± 12.124)		
Week 28: Motor Skills- Gross (n=12,26)	-3.05 (± 15.068)	7.78 (± 21.604)		
Week 40: Communication- Expressive (n=15,32)	-2.35 (± 10.521)	-3.74 (± 12.846)		
Week 40: Communication- Receptive (n=15,32)	0.31 (± 22.511)	-8.32 (± 29.716)		
Week 40: Communication- Written (n=14,32)	-5.39 (± 14.066)	-13.31 (± 15.173)		
Week 40: DLS- Community (n=15,31)	-2.29 (± 13.856)	-9.72 (± 15.988)		
Week 40: DLS- Domestic (n=15,32)	4.40 (± 27.464)	-4.53 (± 27.189)		
Week 40: DLS- Personal (n=15,32)	-5.54 (± 14.516)	-4.33 (± 11.630)		
Week 40: Socialization- Coping Skills (n=15,32)	-11.75 (± 18.650)	-7.31 (± 22.758)		
Week 40: Socialization- IR (n=15,32)	-5.47 (± 13.597)	-6.38 (± 18.307)		
Week 40: Socialization- PLT (n=15,32)	1.83 (± 18.194)	-1.20 (± 19.009)		
Week 40: Motor Skills- Fine (n=12,26)	-3.51 (± 10.891)	-4.04 (± 14.407)		
Week 40: Motor Skills- Gross (n=12,27)	-9.01 (± 18.404)	1.75 (± 18.235)		
Week 52: Communication- Expressive (n=15,32)	-4.87 (± 13.094)	-5.22 (± 14.616)		
Week 52: Communication- Receptive (n=15,32)	5.58 (± 18.225)	-10.14 (± 29.190)		
Week 52: Communication- Written (n=15,32)	-11.22 (± 10.973)	-13.90 (± 16.079)		
Week 52: DLS- Community (n=14,32)	-6.46 (± 13.154)	-7.10 (± 18.149)		
Week 52: DLS- Domestic (n=15,32)	-6.81 (± 28.704)	-8.64 (± 27.817)		
Week 52: DLS- Personal (n=15,32)	-3.64 (± 11.626)	-5.79 (± 15.032)		
Week 52: Socialization- Coping Skills (n=15,32)	-11.26 (± 19.505)	-6.54 (± 20.142)		
Week 52: Socialization- IR (n=15,32)	-8.53 (± 12.960)	-4.46 (± 17.892)		

Week 52: Socialization- PLT (n=15,32)	1.95 (± 25.499)	-0.83 (± 15.499)		
Week 52: Motor Skills- Fine (n=12,26)	-8.58 (± 8.790)	-4.67 (± 15.370)		
Week 52: Motor Skills- Gross (n=12,27)	-14.54 (± 21.617)	2.46 (± 18.655)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of V-Scale Scores of Sub-domains of the Vineland Adaptive Behavior Scales, Second Edition (VABS-II) at Weeks 16, 28, 40 and 52

End point title	Change From Baseline of V-Scale Scores of Sub-domains of the Vineland Adaptive Behavior Scales, Second Edition (VABS-II) at Weeks 16, 28, 40 and 52

End point description:

The VABS-II test measures adaptive behaviors, including the ability to cope with environmental changes, to learn new everyday skills, and to demonstrate independence. This test measures the following 5 key domains: communication, daily living skills, socialization, motor skills, and the adaptive behavior composite (a composite of the other 4 domains). The V-scale scores represent a score (mean = 15 and standard deviation of 3; range: 1-24) on which higher scores indicate a higher level of adaptive functioning. A positive change value indicates improvement in adaptive functioning. In the below table, "IR" indicates interpersonal relationship; "PLT" indicates play and leisure time and "DLS" indicates daily living skills. In the below table, "n" signifies subjects who were evaluable for the specified category, respectively. ITT population included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline, Week 16, Week 28, Week 40 and Week 52

End point values	No IT Treatment	IT Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	34		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 16: Communication- Expressive (n=15,33)	-0.1 (± 1.81)	-0.4 (± 2.05)		
Week 16: Communication- Receptive (n=15,33)	-0.3 (± 1.84)	-0.7 (± 1.85)		
Week 16: Communication- Written (n=15,33)	-0.7 (± 1.83)	-1.1 (± 2.87)		
Week 16: DLS- Community (n=15,33)	-0.3 (± 1.28)	-0.7 (± 2.05)		
Week 16: DLS- Domestic (n=15,33)	-0.3 (± 2.61)	-0.7 (± 1.93)		
Week 16: DLS- Personal (n=15,33)	-1.2 (± 3.23)	-1.2 (± 2.34)		
Week 16: Socialization- Coping Skills (n=15,32)	-0.6 (± 1.80)	-0.4 (± 1.46)		
Week 16: Socialization- IR (n=15,33)	-0.5 (± 1.46)	-0.3 (± 1.55)		
Week 16: Socialization- PLT (n=15,33)	0.2 (± 2.37)	-0.4 (± 1.62)		
Week 16: Motor Skills- Fine (n=12,27)	0.3 (± 1.36)	-0.1 (± 1.33)		
Week 16: Motor Skills- Gross (n=12,28)	-0.3 (± 1.61)	0.0 (± 2.00)		

Week 28: Communication- Expressive (n=15,30)	0.0 (± 2.00)	-0.3 (± 2.20)		
Week 28: Communication- Receptive (n=15,30)	-0.1 (± 2.40)	-0.1 (± 1.17)		
Week 28: Communication- Written (n=15,30)	-0.6 (± 2.41)	-1.2 (± 2.04)		
Week 28: DLS- Community (n=15,30)	-0.7 (± 1.75)	-0.7 (± 1.95)		
Week 28: DLS- Domestic (n=15,30)	0.4 (± 2.75)	-0.4 (± 2.11)		
Week 28: DLS- Personal (n=15,30)	0.6 (± 3.50)	-0.6 (± 2.21)		
Week 28: Socialization- Coping Skills (n=15,30)	0.1 (± 1.51)	-0.2 (± 1.43)		
Week 28: Socialization- IR (n=15,30)	-0.4 (± 1.84)	0.1 (± 1.49)		
Week 28: Socialization- PLT (n=15,30)	1.1 (± 2.03)	0.2 (± 2.04)		
Week 28: Motor Skills- Fine (n=12,25)	-0.3 (± 1.06)	-0.3 (± 1.62)		
Week 28: Motor Skills- Gross (n=12,26)	-0.2 (± 2.33)	0.5 (± 2.06)		
Week 40: Communication- Expressive (n=15,32)	0.0 (± 1.85)	-0.8 (± 1.76)		
Week 40: Communication- Receptive (n=15,32)	-0.2 (± 2.08)	-0.7 (± 2.07)		
Week 40: Communication- Written (n=14,32)	-0.9 (± 2.59)	-2.6 (± 3.05)		
Week 40: DLS- Community (n=15,31)	-0.6 (± 1.59)	-1.6 (± 1.91)		
Week 40: DLS- Domestic (n=15,32)	0.3 (± 2.72)	-0.7 (± 2.66)		
Week 40: DLS- Personal (n=15,32)	-0.6 (± 2.69)	-0.5 (± 2.09)		
Week 40: Socialization- Coping Skills (n=15,32)	-0.6 (± 1.96)	-0.8 (± 1.80)		
Week 40: Socialization- IR (n=15,32)	-0.8 (± 1.70)	-0.9 (± 1.72)		
Week 40: Socialization- PLT (n=15,32)	0.5 (± 2.10)	-0.4 (± 2.24)		
Week 40: Motor Skills- Fine (n=12,26)	-0.3 (± 1.56)	-0.5 (± 1.79)		
Week 40: Motor Skills- Gross (n=12,27)	-0.8 (± 1.90)	-0.1 (± 2.23)		
Week 52: Communication- Expressive (n=15,32)	-0.5 (± 1.88)	-1.0 (± 2.44)		
Week 52: Communication- Receptive (n=15,32)	0.1 (± 2.00)	-0.9 (± 2.08)		
Week 52: Communication- Written (n=15,32)	-2.1 (± 2.09)	-3.0 (± 3.25)		
Week 52: DLS- Community (n=14,32)	-1.5 (± 1.70)	-1.6 (± 2.46)		
Week 52: DLS- Domestic (n=15,32)	-0.5 (± 2.77)	-0.7 (± 2.40)		
Week 52: DLS- Personal (n=15,32)	-0.1 (± 1.85)	-0.9 (± 2.76)		
Week 52: Socialization- Coping Skills (n=15,32)	-0.7 (± 1.80)	-0.5 (± 1.55)		
Week 52: Socialization- IR (n=15,32)	-1.0 (± 1.65)	-0.6 (± 1.81)		
Week 52: Socialization- PLT (n=15,32)	-0.1 (± 3.38)	-0.4 (± 2.00)		
Week 52: Motor Skills- Fine (n=12,26)	-1.1 (± 1.08)	-0.6 (± 2.06)		
Week 52: Motor Skills- Gross (n=12,27)	-1.5 (± 2.07)	-0.1 (± 2.35)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of V-Scale Scores of Maladaptive Behavior Index and Its Sub-scales at Weeks 16, 28, 40 and 52

End point title	Change From Baseline of V-Scale Scores of Maladaptive Behavior Index and Its Sub-scales at Weeks 16, 28, 40 and 52

End point description:

The VABS-II test measures adaptive behaviors, including the ability to cope with environmental changes, to learn new everyday skills, and to demonstrate independence. Maladaptive behavior index is a composite of the internalizing, externalizing, and other types of undesirable behavior that may interfere with the individual's adaptive functioning. The V-scale scores represent a score (mean = 15 and standard deviation of 3; range: 1-24) on which higher scores indicate a higher level of cognitive ability. A positive change value indicates improvement in adaptive functioning. In the below table, "MBI " indicates Maladaptive Behavior Index, "n" signifies subjects who were evaluable for the specified category, respectively. ITT population included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline, Week 16, Week 28, Week 40 and Week 52

End point values	No IT Treatment	IT Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	34		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 16: MBI (n=12,31)	0.3 (± 1.14)	-0.2 (± 1.18)		
Week 16: MBI- Internalizing (n=14,32)	0.1 (± 2.37)	-0.3 (± 2.31)		
Week 16: MBI- Externalizing (n=13,31)	0.5 (± 1.71)	0.0 (± 1.53)		
Week 28: MBI (n=14,28)	0.3 (± 0.91)	-0.3 (± 1.27)		
Week 28: MBI- Internalizing (n=14,29)	-0.4 (± 1.60)	-0.8 (± 2.11)		
Week 28: MBI- Externalizing (n=14,28)	0.6 (± 1.34)	-0.1 (± 2.01)		
Week 40: MBI (n=14,31)	-0.5 (± 1.40)	-0.3 (± 1.13)		
Week 40: MBI- Internalizing (n=14,31)	-1.0 (± 2.57)	-0.7 (± 2.98)		
Week 40: MBI- Externalizing (n=14,31)	-0.1 (± 1.64)	-0.1 (± 1.29)		
Week 52: MBI (n=14,31)	-0.5 (± 1.45)	-0.5 (± 1.41)		
Week 52: MBI- Internalizing (n=14,31)	-1.1 (± 1.96)	-0.9 (± 2.72)		
Week 52: MBI- Externalizing (n=14,31)	-0.4 (± 2.27)	-0.2 (± 1.69)		

Statistical analyses

No statistical analyses for this end point

Secondary: Observed Maladaptive Levels of Maladaptive Behavior Index and Its Sub-scales of Vineland Adaptive Behavior Scales, Second Edition (VABS-II)

End point title	Observed Maladaptive Levels of Maladaptive Behavior Index and Its Sub-scales of Vineland Adaptive Behavior Scales, Second Edition (VABS-II)

End point description:

The VABS-II test measures adaptive behaviors, including the ability to cope with environmental changes, to learn new everyday skills, and to demonstrate independence. Maladaptive behavior index is a composite of the internalizing, externalizing, and other types of undesirable behavior that may interfere with the individual's adaptive functioning. The V-scale scores represent a score (mean = 15 and standard deviation of 3; range: 1-24) on which higher scores indicate a higher level of cognitive ability. A positive change value indicates improvement in adaptive functioning. In the below table, "MBI " indicates Maladaptive Behavior Index.

End point type	Secondary

End point timeframe:
Baseline, Week 16, Week 28, Week 40 and Week 52

End point values	No IT Treatment	IT Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	34		
Units: Subject				
Baseline: MBI- Average	7	8		
Baseline: MBI- Elevated	5	20		
Baseline: MBI- Clinically Significant	2	5		
Baseline: Internalizing- Average	7	15		
Baseline: Internalizing- Elevated	4	11		
Baseline: Internalizing- Clinically Significant	3	7		
Baseline: Externalizing- Average	8	11		
Baseline: Externalizing- Elevated	5	19		
Baseline: Externalizing- Clinically Significant	1	3		
Week 16: MBI- Average	4	9		
Week 16: MBI- Elevated	8	17		
Week 16: MBI- Clinically Significant	1	6		
Week 16: Internalizing- Average	7	19		
Week 16: Internalizing- Elevated	6	9		
Week 16: Internalizing- Clinically Significant	2	5		
Week 16: Externalizing- Average	7	13		
Week 16: Externalizing- Elevated	7	14		
Week 16: Externalizing- Clinically Significant	0	5		
Week 28: MBI- Average	7	8		
Week 28: MBI- Elevated	7	16		
Week 28: MBI- Clinically Significant	1	5		
Week 28: Internalizing- Average	9	18		
Week 28: Internalizing- Elevated	6	10		
Week 28: Internalizing- Clinically Significant	0	2		
Week 28: Externalizing- Average	10	11		
Week 28: Externalizing- Elevated	5	14		
Week 28: Externalizing- Clinically Significant	0	4		
Week 40: MBI- Average	7	7		
Week 40: MBI- Elevated	8	21		
Week 40: MBI- Clinically Significant	0	4		
Week 40: Internalizing- Average	9	20		
Week 40: Internalizing- Elevated	6	10		
Week 40: Internalizing- Clinically Significant	0	2		
Week 40: Externalizing- Average	9	12		
Week 40: Externalizing- Elevated	6	18		
Week 40: Externalizing- Clinically Significant	0	2		

Week 52: MBI- Average	9	10		
Week 52: MBI- Elevated	6	18		
Week 52: MBI- Clinically Significant	0	4		
Week 52: Internalizing- Average	11	20		
Week 52: Internalizing- Elevated	4	9		
Week 52: Internalizing- Clinically Significant	0	3		
Week 52: Externalizing- Average	10	15		
Week 52: Externalizing- Elevated	5	15		
Week 52: Externalizing- Clinically Significant	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Drug Concentration (Cmax) of Idursulfase After IT administration

End point title	Maximum Observed Drug Concentration (Cmax) of Idursulfase After IT administration[1]

End point description:

The Cmax of idursulfase after IT administration was reported. In the below table, "n" signifies subjects who were evaluable for the specified category, respectively. Pharmacokinetic (PK) population included all subjects who received investigational product and participated in the scheduled PK studies, and for whom at least 1 post-dose PK blood sample was collected.

End point type	Secondary

End point timeframe:

Pre-dose, 30, 60, 120 minutes, 4, 6, 8, 12, 24, 30 and 36 hour (h) post-dose on Weeks 4, 24, and 48

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic parameters were evaluated only for subjects who received active study medication.

End point values	IT Treatment			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Week 4 (n=24)	253.44 (± 686.569)			
Week 24 (n=22)	132.87 (± 147.044)			
Week 48 (n=22)	136.15 (± 127.524)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Drug Concentration (tmax) of Idursulfase After IT administration

End point title	Time to Reach Maximum Drug Concentration (tmax) of Idursulfase After IT administration[2]

End point description:

The tmax of idursulfase after IT administration was reported. In the below table, "n" signifies subjects who were evaluable for the specified category, respectively. PK population included all subjects who received investigational product and participated in the scheduled PK studies, and for whom at least 1 post-dose PK blood sample was collected.

End point type	Secondary

End point timeframe:

Pre-dose, 30, 60, 120 minutes, 4, 6, 8, 12, 24, 30 and 36 hour (h) post-dose on Weeks 4, 24, and 48

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic parameters were evaluated only for subjects who received active study medication.

End point values	IT Treatment			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Hour (h)				
arithmetic mean (standard deviation)				
Week 4 (n=24)	10.07 (± 7.217)			
Week 24 (n=22)	10.37 (± 7.302)			
Week 48 (n=22)	10.18 (± 6.609)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration Versus Time Curve From Zero From the Time of Dosing to the Last Measurable Concentration (AUC0-t) of Idursulfase After IT Administration

End point title	Area Under the Concentration Versus Time Curve From Zero From the Time of Dosing to the Last Measurable Concentration (AUC0-t) of Idursulfase After IT Administration[3]

End point description:

The AUC0-t of idursulfase after IT administration was reported. In the below table, "n" signifies subjects who were evaluable for the specified category, respectively. PK population included all subjects who received investigational product and participated in the scheduled PK studies, and for whom at least 1 post-dose PK blood sample was collected.

End point type	Secondary

End point timeframe:

Pre-dose, 30, 60, 120 minutes, 4, 6, 8, 12, 24, 30 and 36 hour (h) post-dose on Weeks 4, 24, and 48

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic parameters were evaluated only for subjects who received active study medication.

End point values	IT Treatment			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Nanogram*hour per milliliter (ng*h/mL)				
arithmetic mean (standard deviation)				
Week 4 (n=24)	2601 (± 5028.0)			
Week 24 (n=22)	2949 (± 4500.4)			
Week 48 (n=22)	2863 (± 3571.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Half-life (t1/2) of Idursulfase After IT Administration

End point title	Terminal Half-life (t1/2) of Idursulfase After IT Administration[4]

End point description:

The t1/2 of idursulfase after IT administration was reported. In the below table, "n" signifies subjects who were evaluable for the specified category, respectively. PK population included all subjects who received investigational product and participated in the scheduled PK studies, and for whom at least 1 post-dose PK blood sample was collected.

End point type	Secondary

End point timeframe:

Pre-dose, 30, 60, 120 minutes, 4, 6, 8, 12, 24, 30 and 36 hour (h) post-dose on Weeks 4, 24, and 48

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic parameters were evaluated only for subjects who received active study medication.

End point values	IT Treatment			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Hour (h)				
arithmetic mean (standard deviation)				
Week 4 (n=11)	11.39 (± 4.996)			
Week 24 (n=12)	10.68 (± 2.851)			
Week 48 (n=11)	11.52 (± 4.243)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total Body Clearance for Extravascular Administration Divided by the

Fraction of Dose Absorbed (CL/F) of Idursulfase after IT Administration

End point title	Total Body Clearance for Extravascular Administration Divided by the Fraction of Dose Absorbed (CL/F) of Idursulfase after IT Administration[5]

End point description:

The CL/F of idursulfase after IT administration was reported. In the below table, "n" signifies subjects who were evaluable for the specified category, respectively. PK population included all subjects who received investigational product and participated in the scheduled PK studies, and for whom at least 1 post-dose PK blood sample was collected.

End point type	Secondary

End point timeframe:

Pre-dose, 30, 60, 120 minutes, 4, 6, 8, 12, 24, 30 and 36 hour (h) post-dose on Weeks 4, 24, and 48

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic parameters were evaluated only for subjects who received active study medication.

End point values	IT Treatment			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Liter per hour (L/h)				
arithmetic mean (standard deviation)				
Week 4 (n=11)	4.82 (± 1.753)			
Week 24 (n=12)	4.54 (± 2.029)			
Week 48 (n=11)	3.94 (± 1.461)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Concentration of Glycosaminoglycans (GAG) in Cerebrospinal Fluid (CSF) at Week 52

End point title	Change From Baseline in the Concentration of Glycosaminoglycans (GAG) in Cerebrospinal Fluid (CSF) at Week 52

End point description:

Change from baseline in the concentration of GAG in CSF was reported. PK population included all subjects who received investigational product and participated in the scheduled PK studies, and for whom at least 1 post-dose PK blood sample was collected.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	No IT Treatment	IT Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	30		
Units: Nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)	-124.6 (± 905.08)	-961.8 (± 797.01)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentration of Idursulfase in Cerebrospinal Fluid (CSF)

End point title	Concentration of Idursulfase in Cerebrospinal Fluid (CSF)[6]

End point description:

CSF samples were collected via the IDDD or lumbar puncture prior to the injection of Idursulfase-IT. In the below table, "n" signifies subjects who were evaluable for the specified category, respectively and "99999" indicates that the standard deviation was not calculated due to less number of subjects. PK population included all subjects who received investigational product and participated in the scheduled PK studies, and for whom at least 1 post-dose PK blood sample was collected.

End point type	Secondary

End point timeframe:

Pre-dose on Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic parameters were evaluated only for subjects who received active study medication.

End point values	IT Treatment			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 4 (n=31)	0 (± 99999)			
Week 8 (n=29)	552.75 (± 2638.000)			
Week 12 (n=27)	520.29 (± 2096.512)			
Week 16 (n=27)	176.87 (± 572.459)			
Week 20 (n=29)	146.66 (± 553.354)			
Week 24 (n=29)	268.72 (± 979.733)			
Week 28 (n=28)	1471.61 (± 5893.839)			
Week 32 (n=28)	141.16 (± 443.484)			
Week 36 (n=29)	521.63 (± 1524.740)			
Week 40 (n=29)	14436.70 (± 75712.900)			
Week 44 (n=29)	1105.46 (± 5331.560)			

Week 48 (n=27)	678.50 (± 3266.592)			

Statistical analyses

No statistical analyses for this end point

Secondary: Subject Response to Quality of Life EuroQol-5D (EQ-5D) Questionnaire at Week 52

End point title	Subject Response to Quality of Life EuroQol-5D (EQ-5D) Questionnaire at Week 52

End point description:

The EQ-5D provides a descriptive profile and index value for health status. The questionnaire measures 5 dimensions of health status: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each dimension, there are 5 levels of response: no problems, slight problems, moderate problems, severe problems, and unable to do/extreme problems. ITT population included all randomized subjects.

End point type	Secondary

End point timeframe:

Week 52

End point values	No IT Treatment	IT Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	34		
Units: Subject				
Mobility: No problems	9	22		
Mobility: Slight problems	4	7		
Mobility: Moderate problems	1	1		
Mobility: Severe problems	0	0		
Mobility: Unable to do	0	0		
Self-care: No problems	3	6		
Self-care: Slight problems	4	10		
Self-care: Moderate problems	4	7		
Self-care: Severe problems	0	3		
Self-care: Unable to do	3	4		
Usual activities: No problems	8	17		
Usual activities: Slight problems	3	5		
Usual activities: Moderate problems	2	6		
Usual activities: Severe problems	0	1		
Usual activities: Unable to do	1	1		
Pain/discomfort: No problems	6	20		
Pain/discomfort: Slight problems	8	7		
Pain/discomfort: Moderate problems	0	3		
Pain/discomfort: Severe problems	0	0		
Pain/discomfort: Unable to do	0	0		
Anxiety/depression: No problems	11	22		

Anxiety/depression: Slight problems	3	6		
Anxiety/depression: Moderate problems	0	1		
Anxiety/depression: Severe problems	0	1		
Anxiety/depression: Unable to do	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Treatment Emergent Adverse Events (TEAEs)

End point title	Number of Subjects with Treatment Emergent Adverse Events (TEAEs)

End point description:

An adverse event (AE) was any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, or laboratory changes occurring in any phase of a clinical study, whether or not considered investigational product-related. Treatment-emergent AEs for the no IT treatment group were defined as all AEs occurring on or after the date of randomization and at or before the end of the study (EOS) visit. Treatment-emergent AEs for the IT treatment group were defined as all AEs occurring on or after the date of the first IDDD implant surgery or first dose of the investigational product (whichever was earlier) and at or before the EOS visit (+30 days) or 2 weeks after the removal of the last IDDD (whichever was later). Safety population included all randomized subjects with any postrandomization safety assessments, analyzed according to the treatment received.

End point type	Secondary

End point timeframe:

From start of study treatment up to Week 53

End point values	No IT Treatment	IT Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	33		
Units: Subject	14	33		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From start of study treatment up to Week 53	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups	
Reporting group title	No IT Treatment
Reporting group description:	
Subjects aged 3 to less than (<) 18 years received elaprase therapy intravenously as standard of care for 12 months.	
Reporting group title	IT Treatment
Reporting group description:	
Subjects aged 3 to < 18 years received intrathecal (IT) injections of 10 milligram (mg) idursulfase-IT once monthly for 12 months through SOPH-A-PORT Mini S intrathecal drug delivery device (IDDD) along with elaprase therapy.	

Serious adverse events	No IT Treatment	IT Treatment	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 15 (13.33%)	12 / 33 (36.36%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Csf cell count increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Procedural nausea			
subjects affected / exposed	0 / 15 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	0 / 15 (0.00%)	2 / 33 (6.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural vomiting			

subjects affected / exposed	0 / 15 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomeningocele			
subjects affected / exposed	0 / 15 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 15 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrospinal fluid leakage			
subjects affected / exposed	0 / 15 (0.00%)	4 / 33 (12.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	0 / 15 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device failure			
subjects affected / exposed	0 / 15 (0.00%)	2 / 33 (6.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device kink			
subjects affected / exposed	0 / 15 (0.00%)	3 / 33 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fatigue			
subjects affected / exposed	0 / 15 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothermia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammation			
subjects affected / exposed	0 / 15 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 15 (0.00%)	4 / 33 (12.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular complication associated with device			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 15 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Catheter site cellulitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Influenza			
subjects affected / exposed	0 / 15 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	No IT Treatment	IT Treatment	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 15 (93.33%)	33 / 33 (100.00%)	
Vascular disorders			
Diastolic hypertension			
subjects affected / exposed	1 / 15 (6.67%)	4 / 33 (12.12%)	
occurrences (all)	1	7	
Diastolic hypotension			
subjects affected / exposed	1 / 15 (6.67%)	4 / 33 (12.12%)	
occurrences (all)	1	6	
Hypotension			
subjects affected / exposed	0 / 15 (0.00%)	3 / 33 (9.09%)	
occurrences (all)	0	3	
Systolic hypertension			
subjects affected / exposed	1 / 15 (6.67%)	4 / 33 (12.12%)	
occurrences (all)	1	9	
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	0 / 15 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	3	

Device breakage				
subjects affected / exposed	0 / 15 (0.00%)	2 / 33 (6.06%)		
occurrences (all)	0	2		
Device occlusion				
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)		
occurrences (all)	2	0		
Gait disturbance				
subjects affected / exposed	0 / 15 (0.00%)	4 / 33 (12.12%)		
occurrences (all)	0	4		
Implant site effusion				
subjects affected / exposed	0 / 15 (0.00%)	6 / 33 (18.18%)		
occurrences (all)	0	8		
Implant site pain				
subjects affected / exposed	0 / 15 (0.00%)	2 / 33 (6.06%)		
occurrences (all)	0	2		
Implant site swelling				
subjects affected / exposed	0 / 15 (0.00%)	3 / 33 (9.09%)		
occurrences (all)	0	3		
Irritability				
subjects affected / exposed	0 / 15 (0.00%)	4 / 33 (12.12%)		
occurrences (all)	0	4		
Medical device pain				
subjects affected / exposed	0 / 15 (0.00%)	3 / 33 (9.09%)		
occurrences (all)	0	3		
Pain				
subjects affected / exposed	0 / 15 (0.00%)	3 / 33 (9.09%)		
occurrences (all)	0	3		
Puncture site pain				
subjects affected / exposed	1 / 15 (6.67%)	1 / 33 (3.03%)		
occurrences (all)	1	1		
Pyrexia				
subjects affected / exposed	7 / 15 (46.67%)	19 / 33 (57.58%)		
occurrences (all)	10	39		
Vascular complication associated with device				

subjects affected / exposed	3 / 15 (20.00%)	5 / 33 (15.15%)	
occurrences (all)	8	5	
Immune system disorders			
Allergy to animal			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Drug hypersensitivity			
subjects affected / exposed	0 / 15 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	4 / 15 (26.67%)	15 / 33 (45.45%)	
occurrences (all)	4	33	
Epistaxis			
subjects affected / exposed	0 / 15 (0.00%)	3 / 33 (9.09%)	
occurrences (all)	0	3	
Hiccups			
subjects affected / exposed	0 / 15 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	6	
Nasal congestion			
subjects affected / exposed	3 / 15 (20.00%)	7 / 33 (21.21%)	
occurrences (all)	4	10	
Oropharyngeal pain			
subjects affected / exposed	1 / 15 (6.67%)	2 / 33 (6.06%)	
occurrences (all)	1	4	
Rhinorrhoea			
subjects affected / exposed	1 / 15 (6.67%)	8 / 33 (24.24%)	
occurrences (all)	1	10	
Wheezing			
subjects affected / exposed	0 / 15 (0.00%)	3 / 33 (9.09%)	
occurrences (all)	0	5	
Psychiatric disorders			

Abnormal behaviour			
subjects affected / exposed	0 / 15 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Affect lability			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Aggression			
subjects affected / exposed	1 / 15 (6.67%)	4 / 33 (12.12%)	
occurrences (all)	2	4	
Agitation			
subjects affected / exposed	0 / 15 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Anxiety			
subjects affected / exposed	0 / 15 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Communication disorder			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Dysphemia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Impulsive behaviour			
subjects affected / exposed	1 / 15 (6.67%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Insomnia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Self injurious behaviour			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Sleep disorder			
subjects affected / exposed	1 / 15 (6.67%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Social avoidant behaviour			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 15 (6.67%)	2 / 33 (6.06%)	
occurrences (all)	2	2	
Albumin csf increased			
subjects affected / exposed	1 / 15 (6.67%)	3 / 33 (9.09%)	
occurrences (all)	1	3	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Blood calcium decreased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Blood pressure diastolic decreased			
subjects affected / exposed	3 / 15 (20.00%)	8 / 33 (24.24%)	
occurrences (all)	3	26	
Blood pressure diastolic increased			
subjects affected / exposed	2 / 15 (13.33%)	6 / 33 (18.18%)	
occurrences (all)	2	10	
Blood pressure increased			
subjects affected / exposed	2 / 15 (13.33%)	1 / 33 (3.03%)	
occurrences (all)	2	1	
Blood pressure systolic decreased			
subjects affected / exposed	1 / 15 (6.67%)	7 / 33 (21.21%)	
occurrences (all)	1	20	
Blood pressure systolic increased			
subjects affected / exposed	2 / 15 (13.33%)	7 / 33 (21.21%)	
occurrences (all)	3	20	
Blood triglycerides increased			
subjects affected / exposed	1 / 15 (6.67%)	2 / 33 (6.06%)	
occurrences (all)	2	2	
Body temperature decreased			
subjects affected / exposed	0 / 15 (0.00%)	5 / 33 (15.15%)	
occurrences (all)	0	6	
Cardiac murmur			

subjects affected / exposed	1 / 15 (6.67%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Coagulation time prolonged			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Csf cell count increased			
subjects affected / exposed	0 / 15 (0.00%)	4 / 33 (12.12%)	
occurrences (all)	0	5	
Csf glucose decreased			
subjects affected / exposed	1 / 15 (6.67%)	7 / 33 (21.21%)	
occurrences (all)	1	9	
Csf pressure increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Csf protein increased			
subjects affected / exposed	2 / 15 (13.33%)	5 / 33 (15.15%)	
occurrences (all)	2	6	
Csf white blood cell count increased			
subjects affected / exposed	0 / 15 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Electrocardiogram qt prolonged			
subjects affected / exposed	0 / 15 (0.00%)	3 / 33 (9.09%)	
occurrences (all)	0	4	
Eosinophil count increased			
subjects affected / exposed	1 / 15 (6.67%)	5 / 33 (15.15%)	
occurrences (all)	1	7	
Eosinophil percentage increased			
subjects affected / exposed	0 / 15 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	3	
Gamma-Glutamyltransferase increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Haematocrit decreased			
subjects affected / exposed	0 / 15 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	3	

Heart rate decreased				
subjects affected / exposed	3 / 15 (20.00%)	7 / 33 (21.21%)		
occurrences (all)	5	25		
Heart rate increased				
subjects affected / exposed	4 / 15 (26.67%)	7 / 33 (21.21%)		
occurrences (all)	6	17		
Lymphocyte count increased				
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)		
occurrences (all)	1	0		
Monocyte count increased				
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)		
occurrences (all)	1	0		
Neutrophil count increased				
subjects affected / exposed	1 / 15 (6.67%)	3 / 33 (9.09%)		
occurrences (all)	1	3		
Nuclear magnetic resonance imaging abnormal				
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)		
occurrences (all)	1	0		
Oxygen saturation decreased				
subjects affected / exposed	2 / 15 (13.33%)	4 / 33 (12.12%)		
occurrences (all)	2	5		
Platelet count decreased				
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)		
occurrences (all)	1	0		
Protein total decreased				
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)		
occurrences (all)	1	0		
Red blood cell count decreased				
subjects affected / exposed	0 / 15 (0.00%)	2 / 33 (6.06%)		
occurrences (all)	0	3		
Red blood cells csf positive				
subjects affected / exposed	0 / 15 (0.00%)	3 / 33 (9.09%)		
occurrences (all)	0	3		
Respiratory rate decreased				

subjects affected / exposed	1 / 15 (6.67%)	2 / 33 (6.06%)	
occurrences (all)	1	2	
Urine leukocyte esterase positive			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
White blood cell count decreased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
White blood cell count increased			
subjects affected / exposed	1 / 15 (6.67%)	2 / 33 (6.06%)	
occurrences (all)	1	2	
White blood cells urine positive			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 15 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Contusion			
subjects affected / exposed	2 / 15 (13.33%)	1 / 33 (3.03%)	
occurrences (all)	2	1	
Excoriation			
subjects affected / exposed	0 / 15 (0.00%)	3 / 33 (9.09%)	
occurrences (all)	0	4	
Fall			
subjects affected / exposed	0 / 15 (0.00%)	3 / 33 (9.09%)	
occurrences (all)	0	5	
Head injury			
subjects affected / exposed	0 / 15 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Incision site oedema			
subjects affected / exposed	0 / 15 (0.00%)	4 / 33 (12.12%)	
occurrences (all)	0	4	
Incision site pain			

subjects affected / exposed	0 / 15 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Infusion related reaction			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Laceration			
subjects affected / exposed	1 / 15 (6.67%)	2 / 33 (6.06%)	
occurrences (all)	1	2	
Procedural hypertension			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Procedural hypotension			
subjects affected / exposed	1 / 15 (6.67%)	3 / 33 (9.09%)	
occurrences (all)	1	3	
Procedural nausea			
subjects affected / exposed	0 / 15 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Procedural pain			
subjects affected / exposed	0 / 15 (0.00%)	14 / 33 (42.42%)	
occurrences (all)	0	15	
Procedural vomiting			
subjects affected / exposed	0 / 15 (0.00%)	4 / 33 (12.12%)	
occurrences (all)	0	6	
Thermal burn			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Wound secretion			
subjects affected / exposed	0 / 15 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Cardiac disorders			
Dilatation ventricular			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Sinus bradycardia			
subjects affected / exposed	0 / 15 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	3	

Sinus tachycardia			
subjects affected / exposed	1 / 15 (6.67%)	4 / 33 (12.12%)	
occurrences (all)	1	10	
Tachycardia			
subjects affected / exposed	0 / 15 (0.00%)	3 / 33 (9.09%)	
occurrences (all)	0	4	
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	3 / 15 (20.00%)	1 / 33 (3.03%)	
occurrences (all)	3	1	
Cerebrospinal fluid leakage			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Drooling			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	1 / 15 (6.67%)	12 / 33 (36.36%)	
occurrences (all)	1	23	
Intracranial pressure increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Psychomotor hyperactivity			
subjects affected / exposed	1 / 15 (6.67%)	5 / 33 (15.15%)	
occurrences (all)	1	5	
Subdural effusion			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Motion sickness			
subjects affected / exposed	0 / 15 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Otorrhoea			
subjects affected / exposed	2 / 15 (13.33%)	2 / 33 (6.06%)	
occurrences (all)	11	2	
Eye disorders			

Astigmatism			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 15 (6.67%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Abdominal pain upper			
subjects affected / exposed	0 / 15 (0.00%)	3 / 33 (9.09%)	
occurrences (all)	0	3	
Constipation			
subjects affected / exposed	2 / 15 (13.33%)	4 / 33 (12.12%)	
occurrences (all)	3	4	
Dental caries			
subjects affected / exposed	0 / 15 (0.00%)	4 / 33 (12.12%)	
occurrences (all)	0	4	
Diarrhoea			
subjects affected / exposed	2 / 15 (13.33%)	10 / 33 (30.30%)	
occurrences (all)	2	20	
Frequent bowel movements			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	0 / 15 (0.00%)	4 / 33 (12.12%)	
occurrences (all)	0	5	
Swollen tongue			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Teething			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Vomiting			
subjects affected / exposed	3 / 15 (20.00%)	25 / 33 (75.76%)	
occurrences (all)	4	72	
Skin and subcutaneous tissue disorders			

Dermatitis allergic			
subjects affected / exposed	1 / 15 (6.67%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Dermatitis contact			
subjects affected / exposed	1 / 15 (6.67%)	2 / 33 (6.06%)	
occurrences (all)	1	2	
Dermatitis diaper			
subjects affected / exposed	2 / 15 (13.33%)	3 / 33 (9.09%)	
occurrences (all)	4	4	
Dry skin			
subjects affected / exposed	0 / 15 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	3	
Rash			
subjects affected / exposed	1 / 15 (6.67%)	5 / 33 (15.15%)	
occurrences (all)	2	5	
Rash erythematous			
subjects affected / exposed	1 / 15 (6.67%)	2 / 33 (6.06%)	
occurrences (all)	1	2	
Rash generalised			
subjects affected / exposed	1 / 15 (6.67%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Rash maculo-papular			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Rash papular			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Red man syndrome			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Scab			
subjects affected / exposed	0 / 15 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Skin irritation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	

Urticaria			
subjects affected / exposed	2 / 15 (13.33%)	1 / 33 (3.03%)	
occurrences (all)	3	1	
Renal and urinary disorders			
Polyuria			
subjects affected / exposed	1 / 15 (6.67%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Proteinuria			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 15 (6.67%)	3 / 33 (9.09%)	
occurrences (all)	1	3	
Foot deformity			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Joint range of motion decreased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Joint stiffness			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Knee deformity			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Muscle tightness			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	0 / 15 (0.00%)	3 / 33 (9.09%)	
occurrences (all)	0	6	
Toe walking			
subjects affected / exposed	0 / 15 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Trigger finger			

subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Atypical pneumonia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Ear infection			
subjects affected / exposed	4 / 15 (26.67%)	9 / 33 (27.27%)	
occurrences (all)	7	10	
Ear infection fungal			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Fungal infection			
subjects affected / exposed	0 / 15 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Gastroenteritis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis viral			
subjects affected / exposed	1 / 15 (6.67%)	5 / 33 (15.15%)	
occurrences (all)	2	6	
Influenza			
subjects affected / exposed	1 / 15 (6.67%)	2 / 33 (6.06%)	
occurrences (all)	1	3	
Localised infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	5 / 15 (33.33%)	13 / 33 (39.39%)	
occurrences (all)	6	22	
Otitis media			
subjects affected / exposed	1 / 15 (6.67%)	4 / 33 (12.12%)	
occurrences (all)	1	4	
Otitis media acute			
subjects affected / exposed	1 / 15 (6.67%)	1 / 33 (3.03%)	
occurrences (all)	2	1	

Periodontitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Pharyngitis streptococcal			
subjects affected / exposed	1 / 15 (6.67%)	2 / 33 (6.06%)	
occurrences (all)	1	2	
Respiratory tract infection			
subjects affected / exposed	1 / 15 (6.67%)	1 / 33 (3.03%)	
occurrences (all)	1	2	
Rhinitis			
subjects affected / exposed	1 / 15 (6.67%)	3 / 33 (9.09%)	
occurrences (all)	1	4	
Sinusitis			
subjects affected / exposed	1 / 15 (6.67%)	3 / 33 (9.09%)	
occurrences (all)	1	4	
Tinea infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Tinea pedis			
subjects affected / exposed	0 / 15 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Upper respiratory tract infection			
subjects affected / exposed	3 / 15 (20.00%)	11 / 33 (33.33%)	
occurrences (all)	5	15	
Viral pharyngitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 15 (6.67%)	1 / 33 (3.03%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 August 2013	- Modifications to the study schedules of events, in particular: scheduling of serum antibody sampling every 3 months in both treatment groups of the pivotal study and in the separate substudy, instructions concerning subject genotyping requirements, clarification concerning safety follow-up post IT injection, and introduction of serum and CSF albumin testing to monitor permeability of the blood-brain barrier. - Specification that the Expanded Interview Form of the VABS-II be utilized. - Specification that the DAS-II Early Years (Spanish version) only will be used for assessment of eligible Spanish-speaking subjects who, additionally, must be below 7 years 8 months of age at the time of informed consent. - Adjustment to dosing for subjects below 3 years of age; the dose of idursulfase-IT dose was adjusted based on reference brain weights, and introduction of cognitive eligibility criteria for this subject subgroup. - Increased the required duration of prior Elaprase therapy from 3 to 4 months. - Modification of the planned statistical analysis.
16 December 2013	- Allowed a limited number of US subjects randomized to the IT treatment arm of the pivotal study to receive monthly IT doses of idursulfase-IT by lumbar puncture prior to FDA authorization of use of the SOPH-A-PORT Mini S device for the purpose of study drug administration. - Made change to determination of cognitive status for inclusion in the separate substudy. Instead of using a standard (composite) score, a developmental quotient (DQ) was used. The DQ has a wider range than the composite score which has a lower boundary at a value of 55.
09 February 2015	- Adusted the timing of the planned blinded variability assessment to meet the criterion of being conducted "prior to enrollment closure" and not to meet the former criterion of being conducted after approximately one-half of the planned number of subjects (ie, approximately 21 subjects) complete Week 52. - Removed US-specific text, no longer necessary following FDA authorization of investigational use of the SOPH-A-PORT Mini S device, allowing a limited number of US subjects randomized to the IT treatment arm of the pivotal study to receive monthly IT doses of idursulfase-IT by lumbar puncture. - Incorporated FDA input (Advice/Information Request letter of 03 December 2014) concerning the planned statistical analysis, add plans for pharmacokinetic analysis, and made minor corrections/clarifications in the statistical analysis text.
21 December 2015	- Allowed the enrollment of approximately 48 subjects based on a blinded variability assessment. - Update to the text pertaining to the SOPH-A-PORT Mini S IDDD for consistency with the sponsor's other protocols utilizing this device for intrathecal drug delivery. - Clarification of aspects of the study schedule pertaining to analysis of CSF and serum samples.
18 April 2016	- Provided guidance concerning the minimum size of a child to undergo IDDD implantation. - Specified the maximum volume of blood to be collected from a subject by study visit.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported