



Clinical trial results:

An Open Label Extension of Study HGT-HIT-094 Evaluating Long Term Safety and Clinical Outcomes of Intrathecal Idursulfase Administered in Conjunction with ELAPRASE® in Patients with Hunter Syndrome and Cognitive Impairment

Summary

EudraCT number	2014-004143-13
Trial protocol	GB ES FR
Global end of trial date	18 April 2024

Results information

Result version number	v1 (current)
This version publication date	02 November 2024
First version publication date	02 November 2024

Trial information

Trial identification

Sponsor protocol code	SHP609-302
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02412787
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire Human Genetic Therapies, Inc.
Sponsor organisation address	300 Shire Way, Lexington, Massachusetts, United States, 02421
Public contact	Study Director, Takeda, N/A N/A, TrialDisclosures@takeda.com
Scientific contact	Study Director, Takeda, N/A N/A, TrialDisclosures@takeda.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 April 2024
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	18 April 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study was to evaluate the long-term safety of intrathecal (IT) idursulfase-IT along with standard-of-care therapy with elaprase in participants with Hunter Syndrome who completed Study HGT-HIT-094 (NCT02055118).

Protection of trial subjects:

Each participant signed an informed consent form (ICF) before participating in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 April 2015
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: 3
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	United States: 35
Worldwide total number of subjects	56
EEA total number of subjects	9

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	1
Children (2-11 years)	54

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:

Participants took part in the study at 22 investigative sites in Australia, Canada, France, Mexico, Spain, the United Kingdom, and the United States of America (USA) from 14 April 2015 to 18 April 2024.

Pre-assignment

Screening details:

A total of 56 participants with a diagnosis of Hunter Syndrome who completed the Study HGT-HIT-094 (NCT02055118) received idursulfase-IT in conjunction with elaprase therapy.

Period 1

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

Arms

Arm title	Idursulfase-IT
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Arm description:

Participants received 10 milligrams (mg) of idursulfase-IT intrathecally via intrathecal drug delivery device (IDDD) or lumbar puncture (LP) once every 28 days along with standard-of-care therapy with elaprase for 480 weeks. Participants who were younger than 3 years of age received an adjusted dose of 7.5 mg (>8 months to 30 months of age) or 10 mg (>30 months to 3 years of age) of idursulfase-IT.

Arm type	Experimental
Investigational medicinal product name	Elaprase
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Elaprase as standard-of-care for 480 weeks.

Investigational medicinal product name	Idursulfase-IT
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

Idursulfase-IT once every 28 days for 480 weeks.

Number of subjects in period 1	Idursulfase-IT
Started	56
Completed	23
Not completed	33
Termination by Sponsor	21
Termination by Investigator	1
Technical Problems	1

Withdrawal by Subject	9
Reason not Specified	1

Baseline characteristics

Reporting groups

Reporting group title	Idursulfase-IT
Reporting group description:	
Participants received 10 milligrams (mg) of idursulfase-IT intrathecally via intrathecal drug delivery device (IDDD) or lumbar puncture (LP) once every 28 days along with standard-of-care therapy with elaprase for 480 weeks. Participants who were younger than 3 years of age received an adjusted dose of 7.5 mg (>8 months to 30 months of age) or 10 mg (>30 months to 3 years of age) of idursulfase-IT.	

Reporting group values	Idursulfase-IT	Total	
Number of subjects	56	56	
Age Categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	4.89		
standard deviation	± 2.117	-	
Gender categorical			
Units: Subjects			
Male	56	56	
Female	0	0	
Race			
Units: Subjects			
Asian	4	4	
Black or African American	1	1	
White	41	41	
Other	10	10	
Ethnicity			
Units: Subjects			
Hispanic or Latino	14	14	
Not Hispanic or Latino	38	38	
Not Reported	4	4	

Subject analysis sets

Subject analysis set title	Idursulfase-IT 10 mg, Delayed IT
Subject analysis set type	Full analysis

Subject analysis set description:

The Delayed IT group included participants who were randomised to the no IT treatment cohort in Study HGT-HIT-094 and began IT treatment in Study SHP609-302.

Subject analysis set title	Idursulfase-IT 10 mg, Early IT
Subject analysis set type	Full analysis

Subject analysis set description:

The Early IT group included participants who were randomised to the IT treatment cohort in Study HGT-HIT-094 and continued in Study SHP609-302.

Subject analysis set title	Idursulfase-IT 10 mg, Former Substudy
Subject analysis set type	Full analysis

Subject analysis set description:

The Former Substudy group included participants who received IT treatment 5-10 mg in HGT-HIT-094 substudy.

Reporting group values	Idursulfase-IT 10 mg, Delayed IT	Idursulfase-IT 10 mg, Early IT	Idursulfase-IT 10 mg, Former Substudy
Number of subjects	15	32	9
Age Categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	6.31 ± 2.678	4.90 ± 1.414	2.48 ± 0.483
Gender categorical Units: Subjects			
Male	15	32	9
Female	0	0	0
Race Units: Subjects			
Asian	0	4	0
Black or African American	0	1	0
White	12	21	8
Other	3	6	1
Ethnicity Units: Subjects			
Hispanic or Latino	5	8	1
Not Hispanic or Latino	8	23	7
Not Reported	2	1	1

End points

End points reporting groups

Reporting group title	Idursulfase-IT
Reporting group description: Participants received 10 milligrams (mg) of idursulfase-IT intrathecally via intrathecal drug delivery device (IDDD) or lumbar puncture (LP) once every 28 days along with standard-of-care therapy with elaprase for 480 weeks. Participants who were younger than 3 years of age received an adjusted dose of 7.5 mg (>8 months to 30 months of age) or 10 mg (>30 months to 3 years of age) of idursulfase-IT.	
Subject analysis set title	Idursulfase-IT 10 mg, Delayed IT
Subject analysis set type	Full analysis
Subject analysis set description: The Delayed IT group included participants who were randomised to the no IT treatment cohort in Study HGT-HIT-094 and began IT treatment in Study SHP609-302.	
Subject analysis set title	Idursulfase-IT 10 mg, Early IT
Subject analysis set type	Full analysis
Subject analysis set description: The Early IT group included participants who were randomised to the IT treatment cohort in Study HGT-HIT-094 and continued in Study SHP609-302.	
Subject analysis set title	Idursulfase-IT 10 mg, Former Substudy
Subject analysis set type	Full analysis
Subject analysis set description: The Former Substudy group included participants who received IT treatment 5-10 mg in HGT-HIT-094 substudy.	

Primary: Number of Participants With Adverse Events (AEs)

End point title	Number of Participants With Adverse Events (AEs) ^[1]
End point description: An AE is 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. The Safety Population included all the participants in Study SHP609-302 who underwent IDDD implantation or received at least 1 dose of study drug (full or partial).	
End point type	Primary
End point timeframe: Up to 9 years	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Only descriptive analysis was planned for this endpoint.	

End point values	Idursulfase-IT			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: participants	56			

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Observed Serum Concentration (C_{max}) of Idursulfase

End point title	Maximum Observed Serum Concentration (Cmax) of Idursulfase ^[2]
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End point description:

Idursulfase concentrations in serum were determined using a validated Enzyme -Linked Immunosorbent Assay (ELISA) method. Concentration for Cmax is presented in this endpoint. The Pharmacokinetic Population included all the participants in Study SHP609-302 who received study drug and participated in the scheduled pharmacokinetic studies, and for whom at least 1 postdose pharmacokinetic blood sample was collected. Number of subjects analysed indicates the number of participants with data available for analyses.

End point type	Primary
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End point timeframe:

Predose and multiple time points post-dose at Week 100

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analysis was planned for this endpoint.

End point values	Idursulfase-IT 10 mg, Delayed IT	Idursulfase-IT 10 mg, Early IT	Idursulfase-IT 10 mg, Former Substudy	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	10	20	3	
Units: nanogram per millilitre (ng/mL)				
arithmetic mean (standard deviation)	128.19 (± 169.427)	104.89 (± 66.879)	120.23 (± 57.308)	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Clinically Significant Changes in Vital Signs, Laboratory Parameters, and 12-lead Electrocardiogram (ECG) Findings

End point title	Number of Participants With Clinically Significant Changes in Vital Signs, Laboratory Parameters, and 12-lead Electrocardiogram (ECG) Findings ^[3]
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End point description:

Number of participants with clinically significant changes in vital signs (the injection [IT] vital signs and regular vital signs (temperature, pulse, blood pressure [systolic and diastolic], oxygen saturation, and respiration rate), laboratory parameters (chemistry, hematology, urinalysis and CSF values), and 12-lead ECG findings (heart rate, PR interval, QRS interval, QT interval and the corrected QT interval) were collected. The Safety Population included all the participants in Study SHP609-302 who underwent IDDD implantation or received at least 1 dose of study drug (full or partial).

End point type	Primary
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End point timeframe:

Up to 9 years

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analysis was planned for this endpoint.

End point values	Idursulfase-IT			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: participants				
Vital Signs	0			
Laboratory Parameters	0			
12-lead ECG	0			

Statistical analyses

No statistical analyses for this end point

Primary: Percent Change From Baseline in the Concentration of Glycosaminoglycan (GAG) in CSF at Month 67

End point title	Percent Change From Baseline in the Concentration of Glycosaminoglycan (GAG) in CSF at Month 67 ^[4]
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End point description:

The percent change in concentration of GAG in CSF was assessed. The Pharmacokinetic Population included all the participants in Study SHP609-302 who received study drug and participated in the scheduled pharmacokinetic studies, and for whom at least 1 postdose pharmacokinetic blood sample was collected. Number of subjects analysed indicates the number of participants with data available for analyses.

End point type	Primary
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End point timeframe:

Baseline, Month 67

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analysis was planned for this endpoint.

End point values	Idursulfase-IT			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: percent change				
arithmetic mean (standard deviation)	-71.15 (± 17.842)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants who Reported Positive for Anti-idursulfase Antibodies in CSF

End point title	Number of Participants who Reported Positive for Anti-idursulfase Antibodies in CSF ^[5]
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End point description:

The Safety Population included all the participants in Study SHP609-302 who underwent IDDD implantation or received at least 1 dose of study drug (full or partial).

End point type	Primary
End point timeframe:	
Up to 9 years	
Notes:	
[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.	
Justification: Only descriptive analysis was planned for this endpoint.	

End point values	Idursulfase-IT			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: participants	25			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants who Reported Positive for Anti-idursulfase Antibodies in Serum

End point title	Number of Participants who Reported Positive for Anti-idursulfase Antibodies in Serum ^[6]
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End point description:

The Safety Population included all the participants in Study SHP609-302 who underwent IDDD implantation or received at least 1 dose of study drug (full or partial).

End point type	Primary
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End point timeframe:

Up to 9 years

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analysis was planned for this endpoint.

End point values	Idursulfase-IT			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: participants	46			

Statistical analyses

No statistical analyses for this end point

Primary: Percent Change From Baseline in the Concentration of GAG in Urine at Month 67

End point title	Percent Change From Baseline in the Concentration of GAG in Urine at Month 67 ^[7]
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End point description:

The percent change in concentration of GAG in urine was assessed. The Pharmacokinetic Population included all the participants in Study SHP609-302 who received study drug and participated in the

scheduled pharmacokinetic studies, and for whom at least 1 postdose pharmacokinetic blood sample was collected. Number of subjects analysed indicates the number of participants with data available for analyses.

End point type	Primary
End point timeframe:	
Baseline, Month 67	

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analysis was planned for this endpoint.

End point values	Idursulfase-IT			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: percent change				
arithmetic mean (standard deviation)	-32.44 (\pm 29.366)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Differential Ability Scales, Second Edition (DAS-II) Standard Cluster Scores at Month 67

End point title	Change From Baseline in Differential Ability Scales, Second Edition (DAS-II) Standard Cluster Scores at Month 67
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End point description:

DAS-II was used to assess all participants of age 2 years, 6 months or older. DAS-II comprises 2 overlapping batteries. Early Years battery (EYB) was designed for children ages 2 years, 6 months through 6 years, 11 months. The School Age Battery (SAB) was designed for children ages 7 years, 0 months through 17 years, 11months. These batteries are fully co-normed for ages 5 years, 0 months, through 8 years, 11 months. The cluster areas include general conceptual ability (GCA), verbal, nonverbal, spatial, and special nonverbal composite (SNC). The cluster area score represents a score (mean=100 and standard deviation=15) on which higher scores=higher level of cognitive ability. Number of subjects analysed indicates the number of participants with data available for analyses. 'n' indicates the number of participants with data available for analyses for specified category.

End point type	Secondary
End point timeframe:	
Baseline, Month 67	

End point values	Idursulfase-IT			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: score on a scale				
arithmetic mean (standard deviation)				
GCA (n=2)	-6.0 (\pm 8.49)			
Verbal (n=3)	-23.7 (\pm 21.59)			
Nonverbal (n=2)	-20.5 (\pm 7.78)			
Spatial (n=3)	0.3 (\pm 18.88)			

SNC (n=2)	-5.5 (± 6.36)			
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Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Standard Scores of the Vineland Adaptive Behaviour Scales, Second Edition (VABS-II) Domains at Month 67

End point title	Change From Baseline in Standard Scores of the Vineland Adaptive Behaviour Scales, Second Edition (VABS-II) Domains at Month 67
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End point description:

The VABS-II test measures adaptive behaviours, including the ability to cope with environmental changes, to learn new everyday skills, and to demonstrate independence. This test measures the following 4 key domains: communication, daily living skills, socialisation, motor skills, and the adaptive behaviour composite [ABC] (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. The Safety Population included all the participants in Study SHP609-302 who underwent IDDD implantation or received at least 1 dose of study drug (full or partial). Number of subjects analysed indicates the number of participants with data available for analyses.

End point type	Secondary
End point timeframe:	
Baseline, Month 67	

End point values	Idursulfase-IT			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: score on a scale				
arithmetic mean (standard deviation)				
Communication	-13.5 (± 4.95)			
Daily Living Skills	-9.5 (± 0.71)			
Socialisation	-14.5 (± 9.19)			
Motor Skills	11.5 (± 7.78)			
ABC	-13.5 (± 2.12)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Standard Composite Scores of the VABS-II Domains at Month 67

End point title	Change From Baseline in Standard Composite Scores of the VABS-II Domains at Month 67
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End point description:

The VABS-II test measures adaptive behaviours, including the ability to cope with environmental changes, to learn new everyday skills, and to demonstrate independence. This test measures the following 4 key domains: communication, daily living skills, socialisation, motor skills, and the ABC (a composite of the other 4 domains). The ABC score 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. The Safety Population included all the participants in Study SHP609-302 who underwent IDDD implantation or received at least 1 dose of study drug (full or partial). Number of subjects analysed indicates the number of participants available for analyses. 'n' indicates the number of participants with data available for analyses for specified category. '999' indicates that no participants were analysed in the specified category.

End point type	Secondary
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End point timeframe:

Baseline, Month 67

End point values	Idursulfase-IT			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline Age < 6 Years (n=2)	-13.5 (± 2.12)			
Baseline Age ≥ 6 Years (n=0)	999 (± 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Age Equivalents Score of the Differential Ability Scales, Second Edition (DAS-II) at Month 61

End point title	Change From Baseline in Age Equivalents Score of the Differential Ability Scales, Second Edition (DAS-II) at Month 61
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End point description:

DAS-II comprises 2 overlapping batteries; EYB= 2 years,6 months through 6 years,11 months and SAB=7 years,0 months through 17 years,11 months. Core subtests include Verbal Comprehension, Picture Similarities, Naming Vocabulary, Pattern Construction, Matrices and Copying for DAS-II Early Years and Recall of Designs, Word Definitions, Pattern Construction, Matrices, Verbal Similarities, and Sequential and Quantitative Reasoning for DAS-II School Years. Standardized scores were converted to age equivalent scores (AES) to measure ability, skill, and knowledge expressed as age at which most individuals reach same level. Higher score (HS)= greater cognitive ability (CA). Subtests score represent a score (mean=50 and standard deviation of 10) on which HS=higher level of CA. Number of subjects analysed=participants with data available for analyses. 'n'=participants with data available for analyses for specified category.'999'=standard deviation not estimable for a single participant.

End point type	Secondary
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End point timeframe:

Baseline, Month 61

End point values	Idursulfase-IT			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: score on a scale				
arithmetic mean (standard deviation)				
EYB: Verbal Comprehension (n=2)	1.50 (± 1.768)			
EYB: Picture Similarities (n=2)	2.63 (± 2.652)			
EYB: Naming Vocabulary (n=2)	3.13 (± 1.237)			
EYB: Pattern Construction (n=2)	1.38 (± 1.237)			
EYB: Matrices (n=2)	3.38 (± 1.237)			
EYB: Copying (n=2)	1.13 (± 1.591)			
SAB: Recall of Designs (n=1)	0.00 (± 999)			
SAB: Word Definitions (n=1)	-0.25 (± 999)			
SAB: Pattern Construction (n=1)	0.00 (± 999)			
SAB: Matrices (n=1)	2.50 (± 999)			
SAB: Verbal Similarities (n=1)	0.00 (± 999)			
SAB: Sequential & Quantitative Reasoning (n=1)	0.75 (± 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Developmental Quotients (DQ) of the DAS-II at Month 61

End point title	Change From Baseline in Developmental Quotients (DQ) of the DAS-II at Month 61
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End point description:

DAS-II was used to assess all participants of age 2 years, 6 months or older. DAS-II comprises 2 overlapping batteries. EYB was designed for children ages 2 years, 6 months through 6 years, 11 months. The SAB was designed for children ages 7 years, 0 months through 17 years, 11 months. The core subtests include Verbal Comprehension, Picture Similarities, Naming Vocabulary, Pattern Construction, Matrices, and Copying for the DAS-II Early Years and Recall of Designs, Word Definitions, Pattern Construction, Matrices, Verbal Similarities, and Sequential and Quantitative Reasoning for the DAS-II School Years. The DQ was computed as a ratio and expressed as a percentage using the AES divided by the age at testing ($[AES/chronological\ age] \times 100$; range, 0-100). Number of subjects analysed is the number of participants with data available for analyses. 'n'=participants with data available for analysis for specified category. '999'=standard deviation not estimable for a single participant.

End point type	Secondary
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End point timeframe:

Baseline, Month 61

End point values	Idursulfase-IT			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: score on a scale				
arithmetic mean (standard deviation)				

EYB: Verbal Comprehension (n=2)	-27.45 (± 13.223)			
EYB: Picture Similarities (n=2)	-7.75 (± 23.971)			
EYB: Naming Vocabulary (n=2)	-10.95 (± 4.596)			
EYB: Pattern Construction (n=2)	-22.25 (± 7.425)			
EYB: Matrices (n=2)	-9.20 (± 12.021)			
EYB: Copying (n=2)	-34.95 (± 15.627)			
SAB: Recall of Designs (n=1)	-25.90 (± 999)			
SAB: Word Definitions (n=1)	-29.30 (± 999)			
SAB: Pattern Construction (n=1)	-28.50 (± 999)			
SAB: Matrices (n=1)	2.20 (± 999)			
SAB: Verbal Similarities (n=1)	-25.90 (± 999)			
SAB: Sequential & Quantitative Reasoning (n=1)	-19.80 (± 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in T-scores of the Core Subtests DAS-II at Month 61

End point title	Change From Baseline in T-scores of the Core Subtests DAS-II at Month 61
End point description:	
<p>DAS-II was used to assess all participants of age 2 years, 6 months or older. DAS-II comprises 2 overlapping batteries. EYB was designed for children ages 2 years, 6 months through 6 years, 11 months. SAB was designed for children ages 7 years, 0 months through 17 years, 11 months. The CS include Verbal Comprehension, Picture Similarities, Naming Vocabulary, Pattern Construction, Matrices, and Copying for the DAS-II Early Years and Recall of Designs, Word Definitions, Pattern Construction, Matrices, Verbal Similarities, and Sequential and Quantitative Reasoning for the DAS-II School Years. CS score represent a score (mean = 50 and standard deviation of 10) on which higher scores indicate a higher level of cognitive ability. Number of subjects analysed=participants with data available for analyses. 'n'=participants with data available for analyses for specified category. '999'=standard deviation not estimable for a single participant.</p>	
End point type	Secondary
End point timeframe:	
Baseline, Month 61	

End point values	Idursulfase-IT			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: score on a scale				
arithmetic mean (standard deviation)				
EYB: Verbal Comprehension (n=2)	-14.5 (± 9.19)			
EYB: Picture Similarities (n=2)	-6.5 (± 10.61)			
EYB: Naming Vocabulary (n=2)	-8.5 (± 4.95)			

EYB: Pattern Construction (n=2)	-10.0 (± 9.90)			
EYB: Matrices (n=2)	2.5 (± 2.12)			
EYB: Copying (n=2)	-14.0 (± 26.87)			
SAB: Recall of Designs (n=1)	-4.0 (± 999)			
SAB: Word Definitions (n=1)	-28.0 (± 999)			
SAB: Pattern Construction (n=1)	-13.0 (± 999)			
SAB: Matrices (n=1)	-3.0 (± 999)			
SAB: Verbal Similarities (n=1)	-24.0 (± 999)			
SAB: Sequential & Quantitative Reasoning (n=1)	-2.0 (± 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Age Equivalents Score of the VABS-II Sub Domains at Month 67

End point title	Change From Baseline in Age Equivalents Score of the VABS-II Sub Domains at Month 67
End point description:	
The VABS-II test measures adaptive behaviours, including the ability to cope with environmental changes, to learn new everyday skills, and to demonstrate independence. This test measures the following subdomains of 5 key domains: Communication (Receptive, Expressive, Written), Daily Living Skills (Personal, Domestic, Community), Socialisation (Interpersonal Relationships, Play and Leisure Time, Coping Skills), Motor Skills (Gross, Fine). The mean age equivalent score was obtained by averaging out the age-equivalent scores for the all the sub-domains except for Gross and Fine motor skills (range: 0, unbound). The Safety Population included all the participants in Study SHP609-302 who underwent IDDD implantation or received at least 1 dose of study drug (full or partial). Number of subjects analysed indicates the number of participants with data available for analyses.	
End point type	Secondary
End point timeframe:	
Baseline, Month 67	

End point values	Idursulfase-IT			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: score on a scale				
arithmetic mean (standard deviation)				
Communication: Receptive	2.13 (± 0.412)			
Communication: Expressive	2.54 (± 1.591)			
Communication: Written	1.58 (± 1.296)			
Daily Living Skills: Personal	4.50 (± 1.296)			
Daily Living Skills: Domestic	3.42 (± 0.825)			
Daily Living Skills: Community	1.83 (± 0.943)			
Socialisation: Interpersonal Relationships	1.92 (± 4.832)			
Socialisation: Play and Leisure Time	2.25 (± 1.768)			
Socialisation: Coping Skills	0.75 (± 1.296)			
Motor Skills: Gross	9.75 (± 8.721)			

Motor Skills: Fine	2.33 (\pm 0.118)			
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Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in DQ of the VABS-II Sub Domains at Month 67

End point title	Change From Baseline in DQ of the VABS-II Sub Domains at Month 67
End point description:	
<p>The VABS-II test measures adaptive behaviours, including the ability to cope with environmental changes, to learn new everyday skills, and to demonstrate independence. This test measures the following subdomains of 5 key domains: Communication (Receptive, Expressive, Written), Daily Living Skills (Personal, Domestic, Community), Socialisation (Interpersonal Relationships, Play and Leisure Time, Coping Skills), Motor Skills (Gross, Fine). The DQ was computed as a ratio and expressed as a percentage using the age-equivalent score divided by the age at testing ($[\text{age-equivalent score}/\text{chronological age}] \times 100$; range, 0-100). The Safety Population included all the participants in Study SHP609-302 who underwent IDDD implantation or received at least 1 dose of study drug (full or partial). Number of subjects analysed indicates the number of participants with data available for analyses.</p>	
End point type	Secondary
End point timeframe:	
Baseline, Month 67	

End point values	Idursulfase-IT			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: score on a scale				
arithmetic mean (standard deviation)				
Communication: Receptive	-7.30 (\pm 19.375)			
Communication: Expressive	-6.65 (\pm 23.547)			
Communication: Written	-40.15 (\pm 10.677)			
Daily Living Skills: Personal	9.50 (\pm 13.011)			
Daily Living Skills: Domestic	-22.60 (\pm 0.424)			
Daily Living Skills: Community	-27.15 (\pm 16.900)			
Socialisation: Interpersonal Relationships	-26.00 (\pm 44.265)			
Socialisation: Play and Leisure Time	-18.00 (\pm 13.435)			
Socialisation: Coping Skills	-44.65 (\pm 31.183)			
Motor Skills: Gross	47.35 (\pm 66.539)			

Motor Skills: Fine	-19.90 (\pm 6.788)			
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Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in v-Scores of the VABS-II Sub Domains at Month 67

End point title	Change From Baseline in v-Scores of the VABS-II Sub Domains at Month 67
End point description: The VABS-II test measures adaptive behaviours, including the ability to cope with environmental changes, to learn new everyday skills, and to demonstrate independence. This test measures the following subdomains of 5 key domains: Communication (Receptive, Expressive, Written), Daily Living Skills (Personal, Domestic, Community), Socialisation (Interpersonal Relationships, Play and Leisure Time, Coping Skills), Motor Skills (Gross, Fine). 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. The Safety Population included all the participants in Study SHP609-302 who underwent IDDD implantation or received at least 1 dose of study drug (full or partial). Number of subjects analysed indicates the number of participants with data available for analyses.	
End point type	Secondary
End point timeframe: Baseline, Month 67	

End point values	Idursulfase-IT			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: score on a scale				
arithmetic mean (standard deviation)				
Communication: Receptive	-0.5 (\pm 2.12)			
Communication: Expressive	-1.0 (\pm 2.83)			
Communication: Written	-8.0 (\pm 2.83)			
Daily Living Skills: Personal	1.0 (\pm 1.41)			
Daily Living Skills: Domestic	-2.0 (\pm 1.41)			
Daily Living Skills: Community	-5.0 (\pm 1.41)			
Socialisation: Interpersonal Relationships	-3.0 (\pm 5.66)			
Socialisation: Play and Leisure Time	-2.0 (\pm 1.41)			
Socialisation: Coping Skills	-3.5 (\pm 2.12)			
Motor Skills: Gross	2.5 (\pm 2.12)			
Motor Skills: Fine	1.5 (\pm 0.71)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in v-Scale Scores of the VABS-II Maladaptive Behaviour Index and its Subscales at Month 67

End point title	Change From Baseline in v-Scale Scores of the VABS-II Maladaptive Behaviour Index and its Subscales at Month 67
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End point description:

The VABS-II test measures adaptive behaviours, including the ability to cope with environmental changes, to learn new everyday skills, and to demonstrate independence. The maladaptive behaviour index is a composite of the internalizing, externalizing, and other types of undesirable behaviour 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 adaptive functioning. The Safety Population included all the participants in Study SHP609-302 who underwent IDDD implantation or received at least 1 dose of study drug (full or partial). Number of subjects analysed indicates the number of participants with data available for analyses. '999'=standard deviation not estimable for a single participant.

End point type	Secondary
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End point timeframe:

Baseline, Month 67

End point values	Idursulfase-IT			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: score on a scale				
arithmetic mean (standard deviation)				
Maladaptive Behaviour Index	-3.0 (± 999)			
Internalizing	-4.0 (± 999)			
Externalizing	-1.0 (± 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Observed Maladaptive Levels of the VABS-II Maladaptive Behaviour Index and its Subscales at Month 61

End point title	Number of Participants With Observed Maladaptive Levels of the VABS-II Maladaptive Behaviour Index and its Subscales at Month 61
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End point description:

The VABS-II test measures adaptive behaviours, including the ability to cope with environmental changes, to learn new everyday skills, and to demonstrate independence. The maladaptive behaviour index is a composite of the internalizing, externalizing, and other types of undesirable behaviour that may interfere with the individual's adaptive functioning. The Safety Population included all the participants in Study SHP609-302 who underwent IDDD implantation or received at least 1 dose of study drug (full or partial). Number of subjects analysed indicates the number of participants with data available for analyses. Only categories having non-zero values are reported.

End point type	Secondary
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End point timeframe:

Month 61

End point values	Idursulfase-IT			
Subject group type	Reporting group			
Number of subjects analysed	47			
Units: count of participants				
Maladaptive Behaviour Index; Average	7			
Maladaptive Behaviour Index; Elevated	1			
Internalizing; Average	6			
Internalizing; Elevated	2			
Externalizing; Average	2			
Externalizing; Elevated	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Brain Structure Volume as Measured by Magnetic Resonance Imaging (MRI)

End point title	Change From Baseline in Brain Structure Volume as Measured by Magnetic Resonance Imaging (MRI)
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End point description:

Brain structure volume was assessed from brain total intracranial volume, brain total tissue volume, brain total white matter, brain total gray matter, and total CSF volume as measured by MRI. The Safety Population included all the participants in Study SHP609-302 who underwent IDDD implantation or received at least 1 dose of study drug (full or partial). Number of subjects analysed indicates the number of participants with data available for analyses.

End point type	Secondary
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End point timeframe:

Baseline, End of Study (final assessment post Month 109)

End point values	Idursulfase-IT			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: cubic centimetres (cm ³)				
arithmetic mean (standard deviation)				
Brain Total Intracranial Volume	-19.813 (± 70.994)			
Brain Total Tissue Volume	-38.573 (± 134.021)			
Brain Total White Matter Volume	98.180 (± 64.194)			
Brain Total Gray Matter Volume	-136.750 (± 79.547)			
Total CSF Volume	58.480 (± 52.382)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 9 years

Adverse event reporting additional description:

The Safety Population included all the participants in Study SHP609-302 who underwent IDDD implantation or received at least 1 dose of study drug (full or partial).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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Reporting groups

Reporting group title	Idursulfase-IT
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Reporting group description:

Participants received 10 milligrams (mg) of idursulfase-IT intrathecally via intrathecal drug delivery device (IDDD) or lumbar puncture (LP) once every 28 days along with standard-of-care therapy with elaprase for 480 weeks. Participants who were younger than 3 years of age received an adjusted dose of 7.5 mg (>8 months to 30 months of age) or 10 mg (>30 months to 3 years of age) of idursulfase-IT.

Serious adverse events	Idursulfase-IT		
Total subjects affected by serious adverse events			
subjects affected / exposed	48 / 56 (85.71%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Device kink			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Device failure			
subjects affected / exposed	22 / 56 (39.29%)		
occurrences causally related to treatment / all	0 / 32		
deaths causally related to treatment / all	0 / 0		
Device extrusion			

subjects affected / exposed	1 / 56 (1.79%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Device dislocation				
subjects affected / exposed	3 / 56 (5.36%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Device deployment issue				
subjects affected / exposed	1 / 56 (1.79%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Device breakage				
subjects affected / exposed	4 / 56 (7.14%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Asthenia				
subjects affected / exposed	1 / 56 (1.79%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular complication associated with device				
subjects affected / exposed	7 / 56 (12.50%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	10 / 56 (17.86%)			
occurrences causally related to treatment / all	0 / 12			
deaths causally related to treatment / all	0 / 0			
Medical device site reaction				
subjects affected / exposed	1 / 56 (1.79%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injection site swelling				

subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Inflammation			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Implant site effusion			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypothermia			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device misuse			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device malfunction			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperthermia			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			

subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anaphylactic reaction			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Testicular torsion			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchospasm			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Asthma			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Acute respiratory failure			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Adenoidal hypertrophy			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Respiratory distress			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sleep disorder			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Staring			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Albumin CSF increased			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
CSF cell count increased			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
CSF glucose decreased			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

CSF lymphocyte count increased subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
CSF protein increased subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
CSF white blood cell count subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcus test positive subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Foreign body aspiration subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Procedural nausea subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Procedural pain subjects affected / exposed	2 / 56 (3.57%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Procedural vomiting subjects affected / exposed	2 / 56 (3.57%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Pseudomeningocele			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Wound dehiscence			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Aortic valve stenosis			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cerebrospinal fluid leakage			
subjects affected / exposed	12 / 56 (21.43%)		
occurrences causally related to treatment / all	0 / 18		
deaths causally related to treatment / all	0 / 0		
Convulsion			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleocytosis			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Syncope			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Dental caries			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematochezia			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Toothache			

subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthritis reactive			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spondylolisthesis			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Catheter site cellulitis			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Central nervous system infection			

subjects affected / exposed	3 / 56 (5.36%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Clostridium difficile colitis			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Corona virus infection			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Endocarditis			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Campylobacter infection			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bacteraemia			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis viral			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Implant site abscess			

subjects affected / exposed	1 / 56 (1.79%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Implant site infection				
subjects affected / exposed	1 / 56 (1.79%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	3 / 56 (5.36%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Meningitis bacterial				
subjects affected / exposed	2 / 56 (3.57%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Meningitis streptococcal				
subjects affected / exposed	1 / 56 (1.79%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nocardiosis				
subjects affected / exposed	1 / 56 (1.79%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Otitis media				
subjects affected / exposed	1 / 56 (1.79%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Parainfluenzae virus infection				
subjects affected / exposed	1 / 56 (1.79%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				

subjects affected / exposed	2 / 56 (3.57%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory syncytial virus infection				
subjects affected / exposed	1 / 56 (1.79%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 56 (1.79%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal bacteraemia				
subjects affected / exposed	1 / 56 (1.79%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal infection				
subjects affected / exposed	2 / 56 (3.57%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Stenotrophomonas infection				
subjects affected / exposed	1 / 56 (1.79%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Streptococcal sepsis				
subjects affected / exposed	1 / 56 (1.79%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tonsillitis				
subjects affected / exposed	1 / 56 (1.79%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wound infection				

subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Idursulfase-IT		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 56 (100.00%)		
Vascular disorders			
Diastolic hypertension			
subjects affected / exposed	5 / 56 (8.93%)		
occurrences (all)	8		
Systolic hypertension			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	8		
Flushing			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Hypertension			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Hypotension			
subjects affected / exposed	6 / 56 (10.71%)		
occurrences (all)	6		
Diastolic hypotension			
subjects affected / exposed	5 / 56 (8.93%)		
occurrences (all)	8		
General disorders and administration site conditions			
Medical device complication			
subjects affected / exposed	9 / 56 (16.07%)		
occurrences (all)	13		
Irritability			
subjects affected / exposed	11 / 56 (19.64%)		
occurrences (all)	12		
Pain			

subjects affected / exposed	11 / 56 (19.64%)		
occurrences (all)	14		
Pyrexia			
subjects affected / exposed	43 / 56 (76.79%)		
occurrences (all)	168		
Vascular complication associated with device			
subjects affected / exposed	9 / 56 (16.07%)		
occurrences (all)	15		
Catheter site effusion			
subjects affected / exposed	6 / 56 (10.71%)		
occurrences (all)	8		
Catheter site erythema			
subjects affected / exposed	6 / 56 (10.71%)		
occurrences (all)	7		
Catheter site extravasation			
subjects affected / exposed	5 / 56 (8.93%)		
occurrences (all)	6		
Catheter site pain			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	5		
Catheter site swelling			
subjects affected / exposed	6 / 56 (10.71%)		
occurrences (all)	8		
Device breakage			
subjects affected / exposed	6 / 56 (10.71%)		
occurrences (all)	7		
Device malfunction			
subjects affected / exposed	17 / 56 (30.36%)		
occurrences (all)	41		
Device occlusion			
subjects affected / exposed	7 / 56 (12.50%)		
occurrences (all)	14		
Face oedema			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	4		

Fatigue			
subjects affected / exposed	6 / 56 (10.71%)		
occurrences (all)	7		
Gait disturbance			
subjects affected / exposed	13 / 56 (23.21%)		
occurrences (all)	19		
Implant site effusion			
subjects affected / exposed	7 / 56 (12.50%)		
occurrences (all)	9		
Implant site swelling			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Influenza like illness			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Infusion site swelling			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Medical device pain			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	4		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	5 / 56 (8.93%)		
occurrences (all)	6		
Hypersensitivity			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Seasonal allergy			
subjects affected / exposed	7 / 56 (12.50%)		
occurrences (all)	9		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Bronchospasm			

subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Choking			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	4		
Cough			
subjects affected / exposed	40 / 56 (71.43%)		
occurrences (all)	148		
Epistaxis			
subjects affected / exposed	7 / 56 (12.50%)		
occurrences (all)	10		
Nasal congestion			
subjects affected / exposed	24 / 56 (42.86%)		
occurrences (all)	61		
Oropharyngeal pain			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	10		
Productive cough			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	7		
Pulmonary oedema			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Respiratory distress			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Rhinorrhoea			
subjects affected / exposed	25 / 56 (44.64%)		
occurrences (all)	63		
Sleep apnoea syndrome			
subjects affected / exposed	5 / 56 (8.93%)		
occurrences (all)	5		
Upper respiratory tract congestion			
subjects affected / exposed	5 / 56 (8.93%)		
occurrences (all)	5		
Upper-airway cough syndrome			

subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	5		
Wheezing			
subjects affected / exposed	9 / 56 (16.07%)		
occurrences (all)	12		
Adenoidal hypertrophy			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	5		
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	7 / 56 (12.50%)		
occurrences (all)	7		
Insomnia			
subjects affected / exposed	7 / 56 (12.50%)		
occurrences (all)	7		
Dysphemia			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	9		
Attention deficit/hyperactivity disorder			
subjects affected / exposed	6 / 56 (10.71%)		
occurrences (all)	6		
Anxiety			
subjects affected / exposed	13 / 56 (23.21%)		
occurrences (all)	14		
Agitation			
subjects affected / exposed	8 / 56 (14.29%)		
occurrences (all)	10		
Aggression			
subjects affected / exposed	11 / 56 (19.64%)		
occurrences (all)	13		
Abnormal behaviour			
subjects affected / exposed	8 / 56 (14.29%)		
occurrences (all)	15		
Staring			

subjects affected / exposed	5 / 56 (8.93%)		
occurrences (all)	6		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	11 / 56 (19.64%)		
occurrences (all)	19		
Albumin CSF increased			
subjects affected / exposed	12 / 56 (21.43%)		
occurrences (all)	17		
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 56 (8.93%)		
occurrences (all)	6		
Blood bicarbonate decreased			
subjects affected / exposed	8 / 56 (14.29%)		
occurrences (all)	15		
Blood calcium decreased			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Blood pressure diastolic decreased			
subjects affected / exposed	12 / 56 (21.43%)		
occurrences (all)	45		
Blood pressure diastolic increased			
subjects affected / exposed	13 / 56 (23.21%)		
occurrences (all)	24		
Blood pressure increased			
subjects affected / exposed	6 / 56 (10.71%)		
occurrences (all)	7		
Blood pressure systolic decreased			
subjects affected / exposed	14 / 56 (25.00%)		
occurrences (all)	46		
White blood cell count decreased			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	6		
Red blood cells CSF positive			

subjects affected / exposed	7 / 56 (12.50%)		
occurrences (all)	13		
Red blood cell count decreased			
subjects affected / exposed	9 / 56 (16.07%)		
occurrences (all)	10		
Platelet count decreased			
subjects affected / exposed	7 / 56 (12.50%)		
occurrences (all)	7		
Oxygen saturation decreased			
subjects affected / exposed	11 / 56 (19.64%)		
occurrences (all)	27		
Nuclear magnetic resonance imaging brain abnormal			
subjects affected / exposed	6 / 56 (10.71%)		
occurrences (all)	7		
Neutrophil count increased			
subjects affected / exposed	8 / 56 (14.29%)		
occurrences (all)	9		
Neutrophil count decreased			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Heart rate increased			
subjects affected / exposed	15 / 56 (26.79%)		
occurrences (all)	40		
Heart rate decreased			
subjects affected / exposed	15 / 56 (26.79%)		
occurrences (all)	67		
Haemoglobin decreased			
subjects affected / exposed	9 / 56 (16.07%)		
occurrences (all)	10		
Haematocrit decreased			
subjects affected / exposed	8 / 56 (14.29%)		
occurrences (all)	13		
Eosinophil percentage increased			
subjects affected / exposed	6 / 56 (10.71%)		
occurrences (all)	15		

Eosinophil count increased subjects affected / exposed occurrences (all)	12 / 56 (21.43%) 29		
Electrocardiogram QT prolonged subjects affected / exposed occurrences (all)	5 / 56 (8.93%) 7		
Coronavirus test positive subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3		
Cardiac murmur subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 4		
Carbon dioxide decreased subjects affected / exposed occurrences (all)	9 / 56 (16.07%) 12		
CSF white blood cell count increased subjects affected / exposed occurrences (all)	12 / 56 (21.43%) 37		
CSF test abnormal subjects affected / exposed occurrences (all)	4 / 56 (7.14%) 4		
CSF protein increased subjects affected / exposed occurrences (all)	20 / 56 (35.71%) 56		
CSF neutrophil count increased subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3		
CSF glucose decreased subjects affected / exposed occurrences (all)	16 / 56 (28.57%) 45		
CSF cell count increased subjects affected / exposed occurrences (all)	13 / 56 (23.21%) 30		
Body temperature decreased subjects affected / exposed occurrences (all)	12 / 56 (21.43%) 24		

Blood uric acid increased subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3		
Blood triglycerides increased subjects affected / exposed occurrences (all)	13 / 56 (23.21%) 14		
Blood thyroid stimulating hormone increased subjects affected / exposed occurrences (all)	5 / 56 (8.93%) 7		
Blood pressure systolic increased subjects affected / exposed occurrences (all)	14 / 56 (25.00%) 43		
White blood cell count increased subjects affected / exposed occurrences (all)	4 / 56 (7.14%) 4		
Injury, poisoning and procedural complications			
Arthropod bite subjects affected / exposed occurrences (all)	10 / 56 (17.86%) 12		
Contusion subjects affected / exposed occurrences (all)	12 / 56 (21.43%) 18		
Excoriation subjects affected / exposed occurrences (all)	14 / 56 (25.00%) 32		
Fall subjects affected / exposed occurrences (all)	17 / 56 (30.36%) 33		
Head injury subjects affected / exposed occurrences (all)	4 / 56 (7.14%) 4		
Incision site oedema subjects affected / exposed occurrences (all)	10 / 56 (17.86%) 10		
Incision site pain			

subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	4		
Joint injury			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	4		
Laceration			
subjects affected / exposed	9 / 56 (16.07%)		
occurrences (all)	12		
Ligament sprain			
subjects affected / exposed	5 / 56 (8.93%)		
occurrences (all)	5		
Post procedural haemorrhage			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Procedural headache			
subjects affected / exposed	5 / 56 (8.93%)		
occurrences (all)	6		
Procedural hypertension			
subjects affected / exposed	9 / 56 (16.07%)		
occurrences (all)	35		
Procedural hypotension			
subjects affected / exposed	13 / 56 (23.21%)		
occurrences (all)	39		
Procedural nausea			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	4		
Procedural pain			
subjects affected / exposed	33 / 56 (58.93%)		
occurrences (all)	65		
Procedural vomiting			
subjects affected / exposed	7 / 56 (12.50%)		
occurrences (all)	9		
Pseudomeningocele			
subjects affected / exposed	5 / 56 (8.93%)		
occurrences (all)	6		
Scratch			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Thermal burn</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Tooth fracture</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>5 / 56 (8.93%)</p> <p>5</p> <p>3 / 56 (5.36%)</p> <p>3</p> <p>4 / 56 (7.14%)</p> <p>5</p>		
<p>Congenital, familial and genetic disorders</p> <p>Foramen magnum stenosis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Developmental hip dysplasia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>3 / 56 (5.36%)</p> <p>3</p> <p>3 / 56 (5.36%)</p> <p>3</p>		
<p>Cardiac disorders</p> <p>Sinus bradycardia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Sinus tachycardia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Tachycardia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 56 (7.14%)</p> <p>5</p> <p>8 / 56 (14.29%)</p> <p>16</p> <p>4 / 56 (7.14%)</p> <p>5</p>		
<p>Nervous system disorders</p> <p>Psychomotor hyperactivity</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nerve compression</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Lethargy</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Headache</p>	<p>6 / 56 (10.71%)</p> <p>6</p> <p>3 / 56 (5.36%)</p> <p>3</p> <p>7 / 56 (12.50%)</p> <p>9</p>		

subjects affected / exposed	27 / 56 (48.21%)		
occurrences (all)	98		
Febrile convulsion			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	4		
Cerebrospinal fluid retention			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	4		
Carpal tunnel syndrome			
subjects affected / exposed	16 / 56 (28.57%)		
occurrences (all)	19		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 56 (8.93%)		
occurrences (all)	6		
Eosinophilia			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Ear and labyrinth disorders			
Motion sickness			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	4		
Cerumen impaction			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Deafness			
subjects affected / exposed	6 / 56 (10.71%)		
occurrences (all)	7		
Ear pain			
subjects affected / exposed	8 / 56 (14.29%)		
occurrences (all)	10		
Middle ear effusion			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	5		
Otorrhoea			

subjects affected / exposed occurrences (all)	12 / 56 (21.43%) 47		
Tympanic membrane perforation subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3		
Eye disorders			
Astigmatism subjects affected / exposed occurrences (all)	4 / 56 (7.14%) 4		
Conjunctivitis subjects affected / exposed occurrences (all)	8 / 56 (14.29%) 8		
Eye swelling subjects affected / exposed occurrences (all)	5 / 56 (8.93%) 5		
Ocular hyperaemia subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3		
Gastrointestinal disorders			
Umbilical hernia subjects affected / exposed occurrences (all)	4 / 56 (7.14%) 4		
Abdominal pain subjects affected / exposed occurrences (all)	8 / 56 (14.29%) 10		
Abdominal pain upper subjects affected / exposed occurrences (all)	4 / 56 (7.14%) 4		
Constipation subjects affected / exposed occurrences (all)	12 / 56 (21.43%) 18		
Dental caries subjects affected / exposed occurrences (all)	15 / 56 (26.79%) 19		
Diarrhoea			

subjects affected / exposed	30 / 56 (53.57%)		
occurrences (all)	86		
Frequent bowel movements			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	5		
Haematochezia			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Nausea			
subjects affected / exposed	12 / 56 (21.43%)		
occurrences (all)	19		
Retching			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Toothache			
subjects affected / exposed	5 / 56 (8.93%)		
occurrences (all)	6		
Vomiting			
subjects affected / exposed	40 / 56 (71.43%)		
occurrences (all)	182		
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Dermatitis allergic			
subjects affected / exposed	5 / 56 (8.93%)		
occurrences (all)	5		
Dermatitis contact			

subjects affected / exposed	7 / 56 (12.50%)		
occurrences (all)	17		
Dermatitis diaper			
subjects affected / exposed	10 / 56 (17.86%)		
occurrences (all)	13		
Dry skin			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	4		
Eczema			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	4		
Erythema			
subjects affected / exposed	9 / 56 (16.07%)		
occurrences (all)	11		
Rash			
subjects affected / exposed	16 / 56 (28.57%)		
occurrences (all)	22		
Rash erythematous			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	4		
Rash generalised			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	4		
Rash macular			
subjects affected / exposed	5 / 56 (8.93%)		
occurrences (all)	9		
Rash maculo-papular			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	9		
Red man syndrome			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	4		
Scab			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	4		
Swelling face			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Urticaria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 56 (7.14%)</p> <p>5</p> <p>10 / 56 (17.86%)</p> <p>17</p>		
<p>Renal and urinary disorders</p> <p>Enuresis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Proteinuria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 56 (7.14%)</p> <p>5</p> <p>3 / 56 (5.36%)</p> <p>3</p>		
<p>Musculoskeletal and connective tissue disorders</p> <p>Toe walking</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Spondylolisthesis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Spinal disorder</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Scoliosis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pain in extremity</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Neck pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Intervertebral disc protrusion</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Foot deformity</p>	<p>7 / 56 (12.50%)</p> <p>8</p> <p>3 / 56 (5.36%)</p> <p>3</p> <p>3 / 56 (5.36%)</p> <p>4</p> <p>3 / 56 (5.36%)</p> <p>3</p> <p>17 / 56 (30.36%)</p> <p>37</p> <p>4 / 56 (7.14%)</p> <p>6</p> <p>3 / 56 (5.36%)</p> <p>3</p>		

subjects affected / exposed	6 / 56 (10.71%)		
occurrences (all)	6		
Back pain			
subjects affected / exposed	16 / 56 (28.57%)		
occurrences (all)	26		
Arthralgia			
subjects affected / exposed	9 / 56 (16.07%)		
occurrences (all)	14		
Achilles tendon discomfort			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Infections and infestations			
Adenovirus infection			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Tooth infection			
subjects affected / exposed	8 / 56 (14.29%)		
occurrences (all)	8		
Corona virus infection			
subjects affected / exposed	17 / 56 (30.36%)		
occurrences (all)	22		
Croup infectious			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	6		
Ear infection			
subjects affected / exposed	32 / 56 (57.14%)		
occurrences (all)	103		
Fungal skin infection			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Gastroenteritis			
subjects affected / exposed	11 / 56 (19.64%)		
occurrences (all)	13		
Gastroenteritis viral			
subjects affected / exposed	14 / 56 (25.00%)		
occurrences (all)	23		

Hand-foot-and-mouth disease subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3		
Influenza subjects affected / exposed occurrences (all)	18 / 56 (32.14%) 26		
Laryngitis subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 8		
Lower respiratory tract infection subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 10		
Metapneumovirus infection subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3		
Nasopharyngitis subjects affected / exposed occurrences (all)	38 / 56 (67.86%) 126		
Oral herpes subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 6		
Otitis externa subjects affected / exposed occurrences (all)	6 / 56 (10.71%) 8		
Otitis media subjects affected / exposed occurrences (all)	21 / 56 (37.50%) 57		
Otitis media acute subjects affected / exposed occurrences (all)	12 / 56 (21.43%) 16		
Pharyngitis subjects affected / exposed occurrences (all)	5 / 56 (8.93%) 11		
Pharyngitis streptococcal subjects affected / exposed occurrences (all)	10 / 56 (17.86%) 12		

Pneumonia			
subjects affected / exposed	7 / 56 (12.50%)		
occurrences (all)	8		
Respiratory syncytial virus infection			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Respiratory tract infection			
subjects affected / exposed	5 / 56 (8.93%)		
occurrences (all)	9		
Rhinitis			
subjects affected / exposed	5 / 56 (8.93%)		
occurrences (all)	19		
Sinusitis			
subjects affected / exposed	11 / 56 (19.64%)		
occurrences (all)	29		
Staphylococcal infection			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	4		
Tinea pedis			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	5		
Tooth abscess			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	8		
Bronchitis			
subjects affected / exposed	5 / 56 (8.93%)		
occurrences (all)	7		
Upper respiratory tract infection			
subjects affected / exposed	37 / 56 (66.07%)		
occurrences (all)	85		
Urinary tract infection			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	6		
Viral infection			
subjects affected / exposed	8 / 56 (14.29%)		
occurrences (all)	9		

Metabolism and nutrition disorders			
Iron deficiency			
subjects affected / exposed	6 / 56 (10.71%)		
occurrences (all)	6		
Decreased appetite			
subjects affected / exposed	10 / 56 (17.86%)		
occurrences (all)	12		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 May 2016	The following changes were made as per Amendment 2: 1. Extended the treatment duration in the study to 5 years. 2. Specified the maximum volume of blood collected from a participant by study visit.
28 February 2017	The following changes were made as per Amendment 3: 1. Added the option of same-day administration of IV ELAPRASE and idursulfase-IT for participants who had already completed at least 12 months of idursulfase-IT treatment in studies HGT-HIT-094 or SHP609-302. 2. Additional pharmacokinetic assessments were implemented to measure any increase in total systemic exposure to idursulfase under the same-day administration regime. 3. A new category of AE relatedness, related to IV ELAPRASE and/or idursulfase-IT, was added to facilitate the collection and analysis of AEs observed with same-day administration.
09 October 2018	The following changes were made as per Amendment 4: 1. Extended the duration of treatment from a maximum of 5 years to a maximum of 10 years. 2. A description of the lower and upper levels of the Early Years battery for DAS-II was added. 3. A strategy for data integration was added. 4. Language was added regarding planned subgroup analyses.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported