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
This version publication date	02 November 2024
First version publication date	02 November 2024

Trial information

Trial identification

Sponsor protocol code	SHP609-302

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

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	6.31	4.90	2.48
standard deviation	± 2.678	± 1.414	± 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 (Cmax) of Idursulfase

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

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

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]

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

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]

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

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]

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]

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:

[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]

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 (± 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

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 (± 8.49)			
Verbal (n=3)	-23.7 (± 21.59)			
Nonverbal (n=2)	-20.5 (± 7.78)			
Spatial (n=3)	0.3 (± 18.88)			

SNC (n=2)	-5.5 (± 6.36)			

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

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

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

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

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

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

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] × 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

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:

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, 11months.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.

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 (± 0.118)			

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:

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 ([age-equivalent score/chronological age] × 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.

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 (± 19.375)			
Communication: Expressive	-6.65 (± 23.547)			
Communication: Written	-40.15 (± 10.677)			
Daily Living Skills: Personal	9.50 (± 13.011)			
Daily Living Skills: Domestic	-22.60 (± 0.424)			
Daily Living Skills: Community	-27.15 (± 16.900)			
Socialisation: Interpersonal Relationships	-26.00 (± 44.265)			
Socialisation: Play and Leisure Time	-18.00 (± 13.435)			
Socialisation: Coping Skills	-44.65 (± 31.183)			
Motor Skills: Gross	47.35 (± 66.539)			

Motor Skills: Fine	-19.90 (± 6.788)			

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 (± 2.12)			
Communication: Expressive	-1.0 (± 2.83)			
Communication: Written	-8.0 (± 2.83)			
Daily Living Skills: Personal	1.0 (± 1.41)			
Daily Living Skills: Domestic	-2.0 (± 1.41)			
Daily Living Skills: Community	-5.0 (± 1.41)			
Socialisation: Interpersonal Relationships	-3.0 (± 5.66)			
Socialisation: Play and Leisure Time	-2.0 (± 1.41)			
Socialisation: Coping Skills	-3.5 (± 2.12)			
Motor Skills: Gross	2.5 (± 2.12)			
Motor Skills: Fine	1.5 (± 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

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

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

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

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)

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

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

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

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.

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 occurrences (all)	6 / 56 (10.71%) 7		
Gait disturbance subjects affected / exposed occurrences (all)	13 / 56 (23.21%) 19		
Implant site effusion subjects affected / exposed occurrences (all)	7 / 56 (12.50%) 9		
Implant site swelling subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3		
Influenza like illness subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3		
Infusion site swelling subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3		
Medical device pain subjects affected / exposed occurrences (all)	4 / 56 (7.14%) 4		
Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all)	5 / 56 (8.93%) 6		
Hypersensitivity subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3		
Seasonal allergy subjects affected / exposed occurrences (all)	7 / 56 (12.50%) 9		
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 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	12 / 56 (21.43%)			
occurrences (all)	29			
Electrocardiogram QT prolonged				
subjects affected / exposed	5 / 56 (8.93%)			
occurrences (all)	7			
Coronavirus test positive				
subjects affected / exposed	3 / 56 (5.36%)			
occurrences (all)	3			
Cardiac murmur				
subjects affected / exposed	3 / 56 (5.36%)			
occurrences (all)	4			
Carbon dioxide decreased				
subjects affected / exposed	9 / 56 (16.07%)			
occurrences (all)	12			
CSF white blood cell count increased				
subjects affected / exposed	12 / 56 (21.43%)			
occurrences (all)	37			
CSF test abnormal				
subjects affected / exposed	4 / 56 (7.14%)			
occurrences (all)	4			
CSF protein increased				
subjects affected / exposed	20 / 56 (35.71%)			
occurrences (all)	56			
CSF neutrophil count increased				
subjects affected / exposed	3 / 56 (5.36%)			
occurrences (all)	3			
CSF glucose decreased				
subjects affected / exposed	16 / 56 (28.57%)			
occurrences (all)	45			
CSF cell count increased				
subjects affected / exposed	13 / 56 (23.21%)			
occurrences (all)	30			
Body temperature decreased				
subjects affected / exposed	12 / 56 (21.43%)			
occurrences (all)	24			

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

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

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

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

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