Clinical trial results:
A Phase I/II, Randomized, Safety and Ascending Dose Ranging Study of Intrathecal Idursulfase-IT administered in conjunction with intravenous Elaprase in Pediatric Patients with Hunter Syndrome and Cognitive Impairment

Summary

EudraCT number	2010-020048-36
Trial protocol	GB
Global end of trial date	29 October 2012

Results information

Result version number	v1 (current)
This version publication date	21 September 2019
First version publication date	01 January 2015

Trial information

Trial identification

Sponsor protocol code	HGT-HIT-045

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00920647
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire Human Genetic Therapies, Inc.
Sponsor organisation address	300 Shire Way, Lexington, United States, 02421
Public contact	Medical Information, Shire Human Genetic Therapies, 001 866-888-0660 ext.2 , US_ShireHGT_Medicalinformation@shire.com
Scientific contact	Medical Information, Shire Human Genetic Therapies, 001 866-888-0660 ext.2 , US_ShireHGT_Medicalinformation@shire.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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 July 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 October 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the safety and tolerability of ascending doses of idursulfase-IT administered via a surgically implanted intrathecal drug delivery device (IDDD) once monthly for 6 months in pediatric patients with Hunter syndrome who have cognitive impairment and who have previously received and tolerated a minimum of 6 months of treatment with Elaprase® (idursulfase for intravenous administration)

Protection of trial subjects:

This study was conducted in compliance with the United States (US) Food and Drug Administration (FDA) Institutional Review Board (IRB) regulations in 21 Code of Federal Regulations (CFR) 56 and the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines. Cautious dose escalation and rigorous safety monitoring by a DSMB were implemented to ensure patient safety throughout this clinical study.

Background therapy:

All patients, regardless of randomization, received a weekly infusion of Elaprase [0.5 milligram/kilogram, intravenously (IV)].

Evidence for comparator: -

Actual start date of recruitment	18 November 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	30 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 11
Country: Number of subjects enrolled	United Kingdom: 5
Worldwide total number of subjects	16
EEA total number of subjects	5

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	16
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 2 investigational sites from 18 November 2009 to 29 October 2012.

Pre-assignment

Screening details:

Screening of all patients occurred between 0 and 60 days prior to randomization.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Control

Arm description:

Three dose cohorts were planned. Within each dose cohort, patients were randomized to 1 of 2 treatment options: treatment with study drug or no treatment with 4 treated patients per dose group and a total of 4 untreated patients (1-2 untreated patients were assigned in each dose cohort). Untreated patients did not undergo surgical placement of an intrathecal drug delivery device (IDDD) and did not receive Idursulfase-Intrathecal (IT).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Idursulfase IT (1 mg)

Arm description:

The original design of the study was to test the dose levels of 10, 30 and 100 mg. This was based on a calculation of a minimally effective dose around 10 mg, with subsequent dose levels being chosen as increasing half-log steps. During the conduct of the study; however, it became clear that the 10 mg dose elicited a strong pharmacodynamic response, as measured by a dramatic and sustained drop in the cerebrospinal fluid (CSF) glycosaminoglycan (GAG) levels. This indicated the need to explore a lower level as a minimally effective dose level, leading to the introduction of the 1 mg group; replacing the planned 100 mg group. Enrollment of patients in this dose cohort commenced after the last patient had been enrolled in 30 mg dose cohort. Four patients were enrolled in the 1 mg dose cohort, underwent surgical placement of an IDDD, and received 1 mg idursulfase as an IT injection via the IDDD once per month (ie, every 28 days) for 6 months.

Arm type	Experimental
Investigational medicinal product name	Idursulfase
Investigational medicinal product code	
Other name	HGT-2310
Pharmaceutical forms	Injection
Routes of administration	Intrathecal use

Dosage and administration details:

Injected monthly using an intrathecal drug delivery device (IDDD; PORT-A-CATH® II Low Profile™ Intrathecal Implantable Access System)

Arm title	Idursulfase IT (10 mg)

Arm description:

Four patients were enrolled in the 10 mg dose cohort, underwent surgical placement of an IDDD, and received 10 mg idursulfase as an IT injection via the IDDD once per month (ie, every 28 days) for 6 months.

Arm type	Experimental

Investigational medicinal product name	Idursulfase
Investigational medicinal product code	
Other name	HGT-2310
Pharmaceutical forms	Injection
Routes of administration	Intrathecal use

Dosage and administration details:

Injected monthly using an intrathecal drug delivery device (IDDD; PORT-A-CATH® II Low Profile™ Intrathecal Implantable Access System)

Arm title	Idursulfase IT (30 mg)

Arm description:

Four patients were enrolled in the 30 mg dose cohort, underwent surgical placement of an IDDD, and received 30 mg idursulfase as an IT injection via the IDDD once per month (ie, every 28 days) for 6 months.

Arm type	Experimental
Investigational medicinal product name	Idursulfase
Investigational medicinal product code	
Other name	HGT-2310
Pharmaceutical forms	Injection
Routes of administration	Intrathecal use

Dosage and administration details:

Injected monthly using an intrathecal drug delivery device (IDDD; PORT-A-CATH® II Low Profile™ Intrathecal Implantable Access System)

Number of subjects in period 1	Control	Idursulfase IT (1 mg)	Idursulfase IT (10 mg)
Started	4	4	4
Completed	4	4	4

Number of subjects in period 1	Idursulfase IT (30 mg)
Started	4
Completed	4

Baseline characteristics

Reporting groups	
Reporting group title	Control
Reporting group description:	
Three dose cohorts were planned. Within each dose cohort, patients were randomized to 1 of 2 treatment options: treatment with study drug or no treatment with 4 treated patients per dose group and a total of 4 untreated patients (1-2 untreated patients were assigned in each dose cohort). Untreated patients did not undergo surgical placement of an intrathecal drug delivery device (IDDD) and did not receive Idursulfase-Intrathecal (IT).	
Reporting group title	Idursulfase IT (1 mg)
Reporting group description:	
The original design of the study was to test the dose levels of 10, 30 and 100 mg. This was based on a calculation of a minimally effective dose around 10 mg, with subsequent dose levels being chosen as increasing half-log steps. During the conduct of the study; however, it became clear that the 10 mg dose elicited a strong pharmacodynamic response, as measured by a dramatic and sustained drop in the cerebrospinal fluid (CSF) glycosaminoglycan (GAG) levels. This indicated the need to explore a lower level as a minimally effective dose level, leading to the introduction of the 1 mg group; replacing the planned 100 mg group. Enrollment of patients in this dose cohort commenced after the last patient had been enrolled in 30 mg dose cohort. Four patients were enrolled in the 1 mg dose cohort, underwent surgical placement of an IDDD, and received 1 mg idursulfase as an IT injection via the IDDD once per month (ie, every 28 days) for 6 months.	
Reporting group title	Idursulfase IT (10 mg)
Reporting group description:	
Four patients were enrolled in the 10 mg dose cohort, underwent surgical placement of an IDDD, and received 10 mg idursulfase as an IT injection via the IDDD once per month (ie, every 28 days) for 6 months.	
Reporting group title	Idursulfase IT (30 mg)
Reporting group description:	
Four patients were enrolled in the 30 mg dose cohort, underwent surgical placement of an IDDD, and received 30 mg idursulfase as an IT injection via the IDDD once per month (ie, every 28 days) for 6 months.	

Reporting group values	Control	Idursulfase IT (1 mg)	Idursulfase IT (10 mg)
Number of subjects	4	4	4
Age categorical Units: Subjects			
In utero	0	04	

Gender categorical Units: Subjects			
Female	0	0	0
Male	4	4	4
Region of Enrollment Units: Subjects			
United States	3	2	4
United Kingdom	1	2	0

Reporting group values	Idursulfase IT (30 mg)	Total	
Number of subjects	4	16	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	4	16	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	6.91		
standard deviation	± 1.678	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	4	16	
Region of Enrollment Units: Subjects			
United States	2	11	
United Kingdom	2	5	

End points

End points reporting groups

Reporting group title	Control

Reporting group description:

Three dose cohorts were planned. Within each dose cohort, patients were randomized to 1 of 2 treatment options: treatment with study drug or no treatment with 4 treated patients per dose group and a total of 4 untreated patients (1-2 untreated patients were assigned in each dose cohort). Untreated patients did not undergo surgical placement of an intrathecal drug delivery device (IDDD) and did not receive Idursulfase-Intrathecal (IT).

Reporting group title	Idursulfase IT (1 mg)

Reporting group description:

The original design of the study was to test the dose levels of 10, 30 and 100 mg. This was based on a calculation of a minimally effective dose around 10 mg, with subsequent dose levels being chosen as increasing half-log steps. During the conduct of the study; however, it became clear that the 10 mg dose elicited a strong pharmacodynamic response, as measured by a dramatic and sustained drop in the cerebrospinal fluid (CSF) glycosaminoglycan (GAG) levels. This indicated the need to explore a lower level as a minimally effective dose level, leading to the introduction of the 1 mg group; replacing the planned 100 mg group. Enrollment of patients in this dose cohort commenced after the last patient had been enrolled in 30 mg dose cohort. Four patients were enrolled in the 1 mg dose cohort, underwent surgical placement of an IDDD, and received 1 mg idursulfase as an IT injection via the IDDD once per month (ie, every 28 days) for 6 months.

Reporting group title	Idursulfase IT (10 mg)

Reporting group description:

Four patients were enrolled in the 10 mg dose cohort, underwent surgical placement of an IDDD, and received 10 mg idursulfase as an IT injection via the IDDD once per month (ie, every 28 days) for 6 months.

Reporting group title	Idursulfase IT (30 mg)

Reporting group description:

Four patients were enrolled in the 30 mg dose cohort, underwent surgical placement of an IDDD, and received 30 mg idursulfase as an IT injection via the IDDD once per month (ie, every 28 days) for 6 months.

Primary: Number of Serious Adverse Events (SAE)

End point title	Number of Serious Adverse Events (SAE)[1]

End point description:

End point type	Primary

End point timeframe:

6 months

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: The statistical methodology supporting the trial focused on descriptive methods given the early phase and objectives of the trial (primarily evaluation of safety). Summary tables tabulated the mean, standard deviation (SD) or standard error, 95% confidence intervals (CI) for the mean, median, minimum, and maximum values for continuous variables and the number and percentage of patients for categorical variables; a missing category was added as needed.

End point values	Control	Idursulfase IT (1 mg)	Idursulfase IT (10 mg)	Idursulfase IT (30 mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	4	4
Units: events	0	8	3	3

Statistical analyses

No statistical analyses for this end point

Primary: Number of Treatment Emergent Adverse Events (AE)

End point title	Number of Treatment Emergent Adverse Events (AE)[2]

End point description:

ITT patient population

End point type	Primary

End point timeframe:

Baseline to Week 23

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: The statistical methodology supporting the trial focused on descriptive methods given the early phase and objectives of the trial (primarily evaluation of safety). Summary tables tabulated the mean, standard deviation (SD) or standard error, 95% confidence intervals (CI) for the mean, median, minimum, and maximum values for continuous variables and the number and percentage of patients for categorical variables; a missing category was added as needed.

End point values	Control	Idursulfase IT (1 mg)	Idursulfase IT (10 mg)	Idursulfase IT (30 mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	4	4
Units: events	23	147	116	104

Statistical analyses

No statistical analyses for this end point

Primary: Safety: Changes in Cerebrospinal Fluid (CSF) White Blood Cells (WBC)

End point title	Safety: Changes in Cerebrospinal Fluid (CSF) White Blood Cells (WBC)[3]

End point description:

White blood cell count in CSF was monitored throughout the study as a way of assessing any potential inflammation of the meninges induced by idursulfase-IT.

End point type	Primary

End point timeframe:

6 months

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: The statistical methodology supporting the trial focused on descriptive methods given the early phase and objectives of the trial (primarily evaluation of safety). Summary tables tabulated the mean, standard deviation (SD) or standard error, 95% confidence intervals (CI) for the mean, median,

minimum, and maximum values for continuous variables and the number and percentage of patients for categorical variables; a missing category was added as needed.

End point values	Control	Idursulfase IT (1 mg)	Idursulfase IT (10 mg)	Idursulfase IT (30 mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	4	4
Units: events	0	3	1	2

Statistical analyses

No statistical analyses for this end point

Primary: Safety: Development of Anti-idursulfase Antibodies (CSF)

End point title	Safety: Development of Anti-idursulfase Antibodies (CSF)[4]

End point description:

Reflects development of anti-idursulfase antibodies post baseline

End point type	Primary

End point timeframe:

6 months

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: The statistical methodology supporting the trial focused on descriptive methods given the early phase and objectives of the trial (primarily evaluation of safety). Summary tables tabulated the mean, standard deviation (SD) or standard error, 95% confidence intervals (CI) for the mean, median, minimum, and maximum values for continuous variables and the number and percentage of patients for categorical variables; a missing category was added as needed.

End point values	Control	Idursulfase IT (1 mg)	Idursulfase IT (10 mg)	Idursulfase IT (30 mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	4	4
Units: subjects	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Safety: Development of Anti-idursulfase Antibodies (Serum)

End point title	Safety: Development of Anti-idursulfase Antibodies (Serum)[5]

End point description:

End point type	Primary

End point timeframe:

6 months

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: The statistical methodology supporting the trial focused on descriptive methods given the early phase and objectives of the trial (primarily evaluation of safety). Summary tables tabulated the mean, standard deviation (SD) or standard error, 95% confidence intervals (CI) for the mean, median, minimum, and maximum values for continuous variables and the number and percentage of patients for categorical variables; a missing category was added as needed.

End point values	Control	Idursulfase IT (1 mg)	Idursulfase IT (10 mg)	Idursulfase IT (30 mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	4	4
Units: subjects	1	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Clinically Significant Electrocardiogram (ECG) Findings at Any Time During the Study

End point title	Clinically Significant Electrocardiogram (ECG) Findings at Any Time During the Study[6]

End point description:

ECG parameters included: heart rate, sinus rhythm, atrial/ventricular hypertrophy, PR, QRS, QT, and QTc intervals.

End point type	Primary

End point timeframe:

6 months

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: The statistical methodology supporting the trial focused on descriptive methods given the early phase and objectives of the trial (primarily evaluation of safety). Summary tables tabulated the mean, standard deviation (SD) or standard error, 95% confidence intervals (CI) for the mean, median, minimum, and maximum values for continuous variables and the number and percentage of patients for categorical variables; a missing category was added as needed.

End point values	Control	Idursulfase IT (1 mg)	Idursulfase IT (10 mg)	Idursulfase IT (30 mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	4	4
Units: subjects	0	0	1	0

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in CSF Glycosaminoglycans (GAGs)

End point title	Change from Baseline in CSF Glycosaminoglycans (GAGs)

End point description:	
Percent change from Baseline to Week 27.	
End point type	Secondary
End point timeframe:	
Baseline to Week 27	

End point values	Control	Idursulfase IT (1 mg)	Idursulfase IT (10 mg)	Idursulfase IT (30 mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	4	4
Units: Percent change				
arithmetic mean (standard error)	6.68 (± 6.301)	-79.03 (± 5.167)	-90.3 (± 2.917)	-88.87 (± 1.035)

Statistical analyses

No statistical analyses for this end point

Secondary: Level of Idursulfase in the CSF Compartment Resulting From Monthly Idursulfase IT Administrations

End point title	Level of Idursulfase in the CSF Compartment Resulting From Monthly Idursulfase IT Administrations[7]
End point description:	
Samples collected from patients treated at doses of 1 mg and 30 mg, as well as the control group, were below the lower limit of detection of the bioanalytical method (3.13 nanogram/millilitre).	
End point type	Secondary
End point timeframe:	
Week 27 (end of study)	

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Subjects in the control group did not receive Idursulfase-IT, so the concentration of CSF Idursulfase could not be measured in these patients. Samples collected from subjects in the 1 mg group and the 30 mg group were below the lower limit of detection of the bioanalytical method (3.13 ng/mL).

End point values	Idursulfase IT (10 mg)			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: nanogram/millilitre				
arithmetic mean (standard deviation)	6.74 (± 12.02)			

Statistical analyses

No statistical analyses for this end point

Secondary: Concentration of Idursulfase in the Serum After a Single Administration

in Conjunction With Elaprase

End point title	Concentration of Idursulfase in the Serum After a Single Administration in Conjunction With Elaprase[8]

End point description:

Values below lower limit of quantitation (LLOQ) are listed as 0.

End point type	Secondary

End point timeframe:

Week 3

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Subjects in the control group did not receive Idursulfase-IT, so the concentration of serum Idursulfase could not be measured in these patients. Data were not available for the calculations in the patients of 1 mg Idursulfase-IT group at Week 3.

End point values	Idursulfase IT (10 mg)	Idursulfase IT (30 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	3		
Units: minutes*nanogram/millilitre				
arithmetic mean (standard deviation)	140022 (± 45479)	228840 (± 37909)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentration of Idursulfase in Serum After Repeated Doses of Intrathecal Idursulfase-IT Given in Conjunction With Elaprase

End point title	Concentration of Idursulfase in Serum After Repeated Doses of Intrathecal Idursulfase-IT Given in Conjunction With Elaprase[9]

End point description:

End point type	Secondary

End point timeframe:

Week 23

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Subjects in the control group did not receive Idursulfase-IT, so the concentration of serum Idursulfase could not be measured in these patients.

End point values	Idursulfase IT (1 mg)	Idursulfase IT (10 mg)	Idursulfase IT (30 mg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	4	4	
Units: min*ng/mL				
arithmetic mean (standard deviation)	31481 (± 0)	150544 (± 43871)	174247 (± 49795)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Urinary GAGs

End point title	Percent Change From Baseline in Urinary GAGs
End point description: Percent change from Baseline to Week 27.	
End point type	Secondary
End point timeframe: Baseline to Week 27	

End point values	Control	Idursulfase IT (1 mg)	Idursulfase IT (10 mg)	Idursulfase IT (30 mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	4	4
Units: Percent change				
arithmetic mean (standard error)	-7.67 (± 20.82)	37.83 (± 27.971)	-22.38 (± 4.84)	29.7 (± 13.7)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Time of informed consent until 30 days after the patient's end of study visit.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups	
Reporting group title	Control
Reporting group description: Untreated patients	
Reporting group title	Idursulfase Intrathecal (IT) (1 mg)
Reporting group description: -	
Reporting group title	Idursulfase IT (10 mg)
Reporting group description: -	
Reporting group title	Idursulfase IT (30 mg)
Reporting group description: -	

Serious adverse events	Control	Idursulfase Intrathecal (IT) (1 mg)	Idursulfase IT (10 mg)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	3 / 4 (75.00%)	2 / 4 (50.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Device dislocation	Additional description: Untreated control patients did not have the IDDD implanted.		
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Complication of device insertion	Additional description: Untreated control patients did not have the IDDD implanted.		
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device breakage	Additional description: Untreated control patients did not have the IDDD implanted.		

subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device connection issue	Additional description: Untreated control patients did not have the IDDD implanted.		
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device failure	Additional description: Untreated control patients did not have the IDDD implanted.		
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device malfunction	Additional description: Untreated control patients did not have the IDDD implanted.		
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound dehiscence	Additional description: Untreated control patients did not have the IDDD implanted.		
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Implant site infection	Additional description: Untreated control patients did not have the intrathecal drug delivery device (IDDD) implanted.		
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Idursulfase IT (30 mg)		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 4 (50.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Device dislocation	Additional description: Untreated control patients did not have the IDDD implanted.		
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Complication of device insertion	Additional description: Untreated control patients did not have the IDDD implanted.		
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Device breakage	Additional description: Untreated control patients did not have the IDDD implanted.		
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Device connection issue	Additional description: Untreated control patients did not have the IDDD implanted.		
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Device failure	Additional description: Untreated control patients did not have the IDDD implanted.		
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Device malfunction	Additional description: Untreated control patients did not have the IDDD implanted.		

subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wound dehiscence	Additional description: Untreated control patients did not have the IDDD implanted.		
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Implant site infection	Additional description: Untreated control patients did not have the intrathecal drug delivery device (IDDD) implanted.		
subjects affected / exposed	2 / 4 (50.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

Metabolism and nutritionp l

subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	2 / 4 (50.00%)
occurrences (all)	0	0	4
Haematoma			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Catheter related complication			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Catheter site erythema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Catheter site haematoma			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Extravasation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Implant site effusion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Implant site erythema			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Implant site scar			

subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Implant site swelling			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
Infusion site extravasation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 4 (50.00%)	0 / 4 (0.00%)
occurrences (all)	0	4	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Choking			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hypoxia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Nasal congestion			

subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	3	0
Oropharyngeal pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Productive cough			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Rhinorrhoea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Sneezing			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Stridor			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract congestion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Aggression			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	3	0
Agitation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Anxiety			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Personality change			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Staring			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Alanine aminotransferase increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Blood calcium decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Blood chloride increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Blood phosphorus decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Blood pressure decreased			
subjects affected / exposed	0 / 4 (0.00%)	2 / 4 (50.00%)	2 / 4 (50.00%)
occurrences (all)	0	4	5
Blood pressure diastolic decreased			
subjects affected / exposed	0 / 4 (0.00%)	2 / 4 (50.00%)	3 / 4 (75.00%)
occurrences (all)	0	6	9
Blood pressure diastolic increased			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	1	1	2
Blood pressure increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	2
Blood pressure systolic decreased			

subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	2 / 4 (50.00%)
occurrences (all)	0	7	3
Blood pressure systolic increased			
subjects affected / exposed	1 / 4 (25.00%)	2 / 4 (50.00%)	2 / 4 (50.00%)
occurrences (all)	1	10	5
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Blood triglycerides increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Body temperature decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	0	3	1
Body temperature increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
CSF cell count increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	0	2	1
CSF glucose decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	2 / 4 (50.00%)
occurrences (all)	0	0	2
CSF protein increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	0	2	1
CSF white blood cell count increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Cardiac murmur			

subjects affected / exposed	0 / 4 (0.00%)	2 / 4 (50.00%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Haematocrit decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Haemoglobin decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Heart rate decreased			
subjects affected / exposed	1 / 4 (25.00%)	2 / 4 (50.00%)	1 / 4 (25.00%)
occurrences (all)	1	8	2
Heart sounds abnormal			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Mean cell volume abnormal			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
Neutrophil count decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Oxygen saturation decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
PCO2 decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Protein total decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	2 / 4 (50.00%)
occurrences (all)	0	1	5
Red blood cell count decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Red blood cells CSF positive			

subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Respiratory rate decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Respiratory rate increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Thyroxine decreased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Vitamin D decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Agitation postoperative			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Arthropod bite			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Burns first degree			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Contusion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	2 / 4 (50.00%)
occurrences (all)	0	0	2
Device malfunction			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Drug delivery system malfunction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Excoriation			

subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
Medical device complication			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Procedural complication			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Procedural pain			
subjects affected / exposed	3 / 4 (75.00%)	4 / 4 (100.00%)	4 / 4 (100.00%)
occurrences (all)	3	5	7
Procedural site reaction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	2 / 4 (50.00%)
occurrences (all)	0	0	2
Scratch			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Skin laceration			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Suture related complication			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Thermal burn			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Traumatic lumbar puncture			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Congenital, familial and genetic disorders			
Bicuspid aortic valve			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			

Atrioventricular block first degree			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Cyanosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Left atrial hypertrophy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Left ventricular hypertrophy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Mitral valve incompetence			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Mitral valve prolapse			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Tachycardia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Clonus			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Dyskinesia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	3 / 4 (75.00%)
occurrences (all)	1	0	3
Hyperreflexia			

subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Psychomotor hyperactivity			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
Pyramidal tract syndrome			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Sensory integrative dysfunction			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Syncope			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Eosinophilia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Lymphadenopathy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Microcytosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Middle ear effusion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Motion sickness			

subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Otorrhoea			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	2 / 4 (50.00%)
occurrences (all)	0	2	2
Tympanic membrane disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Ocular hyperaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Constipation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 4 (0.00%)	2 / 4 (50.00%)	1 / 4 (25.00%)
occurrences (all)	0	4	2
Dysphagia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 4 (0.00%)	2 / 4 (50.00%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Umbilical hernia			

subjects affected / exposed	1 / 4 (25.00%)	2 / 4 (50.00%)	3 / 4 (75.00%)
occurrences (all)	1	6	7
Skin and subcutaneous tissue disorders			
Dermatitis diaper			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Dry skin			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Eczema			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Erythema			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Pruritus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	2 / 4 (50.00%)
occurrences (all)	0	0	2
Swelling face			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Urticaria			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Neck pain			

subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Scoliosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Tendon disorder			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Toe walking			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Infections and infestations			
Anorectal infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Ear infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Eye infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Herpes zoster			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Implant site infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Otitis media			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0

Rhinitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 4 (25.00%)	3 / 4 (75.00%)	3 / 4 (75.00%)
occurrences (all)	1	3	3
Urinary tract infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Dehydration			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Pica			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Idursulfase IT (30 mg)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)		
Vascular disorders			
Blood pressure fluctuation			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Flushing			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Haematoma			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Surgical and medical procedures			

Tooth extraction			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Catheter related complication			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	2		
Catheter site erythema			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Catheter site haematoma			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Extravasation			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Implant site effusion			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Implant site erythema			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Implant site scar			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Implant site swelling			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Infusion site extravasation			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	2		
Oedema peripheral			

subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	3		
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Choking			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Cough			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	3		
Epistaxis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Hypoxia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Nasal congestion			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Productive cough			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Sneezing			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Stridor			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Upper respiratory tract congestion			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Aggression			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Agitation			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Anxiety			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Personality change			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Staring			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Investigations			
Activated partial thromboplastin time prolonged			

subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Alanine aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Blood calcium decreased			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Blood chloride increased			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Blood phosphorus decreased			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Blood pressure decreased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Blood pressure diastolic decreased			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	10		
Blood pressure diastolic increased			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	5		
Blood pressure increased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Blood pressure systolic decreased			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	6		
Blood pressure systolic increased			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	8		
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		

Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Blood triglycerides increased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Body temperature decreased			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Body temperature increased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
CSF cell count increased			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	2		
CSF glucose decreased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
CSF protein increased			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	2		
CSF white blood cell count increased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Cardiac murmur			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	2		
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Haematocrit decreased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Haemoglobin decreased			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Heart rate decreased			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Heart sounds abnormal			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Mean cell volume abnormal			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Neutrophil count decreased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Oxygen saturation decreased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
PCO2 decreased			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Protein total decreased			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Red blood cell count decreased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Red blood cells CSF positive			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Respiratory rate decreased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Respiratory rate increased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Thyroxine decreased			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Vitamin D decreased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Agitation postoperative			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Arthropod bite			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Burns first degree			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Contusion			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Device malfunction			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Drug delivery system malfunction			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Excoriation			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Medical device complication			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Procedural complication			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Procedural pain			

subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Procedural site reaction			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Scratch			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Skin laceration			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Suture related complication			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Thermal burn			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Traumatic lumbar puncture			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Congenital, familial and genetic disorders			
Bicuspid aortic valve			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Cyanosis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Left atrial hypertrophy			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Left ventricular hypertrophy			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Mitral valve incompetence			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Mitral valve prolapse			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Tachycardia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Clonus			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	5		
Dyskinesia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Hyperreflexia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Psychomotor hyperactivity			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Pyramidal tract syndrome			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Sensory integrative dysfunction			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)			

Syncope			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Eosinophilia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Lymphadenopathy			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Microcytosis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Middle ear effusion			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Motion sickness			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Otorrhoea			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Tympanic membrane disorder			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Eye disorders			
Ocular hyperaemia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			

Abdominal distension			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Dysphagia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Umbilical hernia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Dermatitis diaper			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Dry skin			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Eczema			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Erythema			

subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Swelling face			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Urticaria			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Neck pain			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Scoliosis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Tendon disorder			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Toe walking			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Anorectal infection			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Ear infection			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Eye infection			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Gastrointestinal infection			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Herpes zoster			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Implant site infection			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Otitis media			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Rhinitis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	4 / 4 (100.00%)		
occurrences (all)	5		
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Dehydration			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Pica			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2008	Clarify information and text related to: • Safety-related stopping rules (such that if any patient experienced a study drug-related, life-threatening [Grade 4] AE or death, or if 2 or more patients experienced a Grade 3 AE considered possibly or probably related to study drug by the sponsor, then the site would be instructed to halt idursulfase-IT administration to all patients).
25 July 2008	• Allow for surgical insertion of the IDDD (PORT-A-CATH device); • Allow for the addition of 4 patients to participate in screening, baseline, and end of study procedures, but not to receive the IDDD or study drug; • Clarify information and text related to: • Safety-related stopping rules (such that if any patient experienced a study drug-related, life-threatening [Grade 4] AE or death, or if 2 or more patients experienced a Grade 3 AE considered possibly or probably related to study drug by the sponsor, then the site would be instructed to halt idursulfase-IT administration to all patients). • Updating and reformatting of references.
29 October 2008	• Incorporated an independent review by a DSMB • Allow for proteomic marker testing in plasma and CSF • Clarify information and text related to: • The removal of the abbreviation I2S for the drug product idursulfase • The definition of infusion-related reactions and SAE reporting
21 January 2009	• Clarify information and text related to: • Secondary endpoints (minor change in text); • Inclusion criteria (added an alternate way to show evidence of early stage Hunter syndrome-related CNS involvement, specifically if the patient is assessed to be between 2 and 3 standard deviations below the mean overall IQ of the healthy population); • Study procedures (clarification of study visit dates, change in text for hearing assessments, addition of X-ray to confirm placement of the device, addition of text regarding neurological screening assessments performed on Day 7); • Clarify that the safety analysis population is to include all enrolled patients; • Include information about an extension study.
08 July 2009	• Clarify information and text related to: • Removal of redundant text from inclusion criterion 3b; • Removal of the IDDD in patients who discontinue participation in the study; • CSF sampling and measurement of opening pressure; • Study procedures (components of physical examinations, timing of vision and hearing assessment, serum chemistry assessments, urinary GAG assessments, auditory brainstem response, surgical implantation of the IDDD [suture removal, removal of a nonfunctional device], performance of X-ray, timing of neurological assessments, neurodevelopmental/behavioral assessments.)

21 October 2009	• Clarify information and text related to: • Dose escalation guidelines (role of DSMB); • Inclusion criterion 1b (add documented mutation of iduronate-2 sulfatase gene as part of eligibility for the trial); • Inclusion criteria 3 (relating to increase in the acceptable range of IQ values – changed from "between 2 and 3 standard deviations below the mean" to "from 2 to 3.5 standard deviations below the mean" • Study procedures (timing of serum chemistry assessments, BRIEF neurobehavioral assessment, removal of local postoperative neurological examination at week 2); • Update to Medical Monitor's contact information.
23 March 2010	• Clarify information and text related to: • Inclusion criteria (increase the acceptable IQ range and description of cognitive impairment in terms of IQ score: an IQ between 77 and 47 (corresponding to a level between 1.5 and 3.5 standard deviations below the mean overall IQ of the healthy population) • Exclusion criteria (revision of IQ criteria consistent with change to inclusion criterion above, minor change to clarify that opening CSF pressure upon lumbar puncture may not exceed 30.0 cm H20); • Study procedures (revise timing of baseline assessments to precede enrollment/randomization and to be completed in conjunction with confirmatory screening assessments, revise the naming of study visits, institute a delay between randomization and the initial study week for untreated patients to align elapsed time on study with that of treated patients, institute an interim safety follow-up telephone contact for untreated patients, increase the allowable window for the screening visit neurodevelopmental assessments); • Corrections or clarifications to terminologies. • Revise safety objectives of the study to emphasize that the study's primary objective and respective endpoint is the investigation of the safety and tolerability of idursulfase-IT; • Allow for more than one main clinical site; • Clarify communication between the medical monitor and investigator(s) of reviewed patient safety data.
07 June 2010	• Clarify information and text related to: • Feed back from the clinical site regarding the labels describing timing of the study periods and study assessments. The study assessment weeks were modified to revert numbering and titles of study weeks to that described in Amendment 6; • Study procedures (clarify timing of randomization (Day 0), eliminate Day 2 neurological exam, correct timing of the brief neurodevelopmental assessment; • Revise text requiring that all deaths during the study be reported to the IEC/IRB. Expedited reports of study drug-related deaths are to be provided to the IRB; however, reporting of nonrelated deaths is not required by IEC/IRB, and the statement that details reporting unrelated deaths was stricken from the protocol.
16 August 2010	• Clarify information and text related to: • Inclusion criteria modified to include: • Pediatric patients from 3 to 17 years of age, inclusive, with Hunter syndrome who have cognitive impairment defined as a measurable IQ of 77 or less • Flexibility in the protocol language such that potentially eligible patients with inadequate cognitive status for full neurodevelopmental testing may still be acceptable for participation in the study; • Study procedures (addition of the BSID-III to the protocol as an alternative to the DASII) • Text was added describing the classification of AEs with respect to study drug, study drug administration device, and associated procedures. • Introductory text was updated with currently available information concerning the safety profiles of idursulfase-IT and Elaprase derived from the current edition of the Idursulfase-IT Investigator's Brochure. • Minor edits and/or corrections were made to more closely align in-text descriptions of study procedures with tabulations and footnotes in the Schedules of Study Procedures.

09 February 2011	• Clarify information and text related to: • The period of time for conduct of screening assessments was extended from 30 days to 60 days; • The timing of patient enrollment during the dose escalation process was modified such that the third and fourth patients within a dose group could both be enrolled upon confirmation of safety following administration of the first dose of study drug to the second patient (previous versions of the protocol required that dosing of the fourth patient be delayed until the third patient had received the first dose of study drug).
26 April 2011	• Clarify information and text related to: • The timing of vital sign and urine GAG assessments for treated patients; • Updated safety information concerning idursulfase-IT and Elaprase from ongoing studies; • Introduce an additional dose group (Group 4) of 4 patients to receive 6 monthly doses of idursulfase–IT at a revised lowest planned dose level (1 mg) to be administered during the study. The addition of this new dose group was intended to explore the lower end of the dose-response relationship.
20 July 2011	• Clarify information and text related to: • Operational aspects of the study, most notably, adjustments to the timing of PK evaluations; • Updated safety information concerning IDDD and an appendix intended to assist in investigation and management in the event of a mechanical IDDD failure; • Clarify that the 2 no-treatment patients originally intended for the 100 mg cohort would instead be randomized as part of the 1 mg cohort.
10 April 2012	• To eliminate evaluation of idursulfase-IT at the highest initially planned dose level of 100 mg • Clarify information and text related to: • Operational aspects of the study, including clarifications to the timing of pre-treatment urine sample and PK blood sample collection, allowance of a time window for vital signs collection • To include up-to-date nonclinical and clinical safety data derived from the annual update of the Idursulfase-IT Investigator's Brochure (data cutoff date 19 January 2012) • To remove information specific to the Smith's Medical IDDD in relation to investigation and management of device failures • To define the Intent-to-Treat (ITT) analysis population as all randomized patients.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Untreated control subjects were not implanted with an IDDD. Concentration of idursulfase in all CSF samples post single dose of idursulfase-IT were below the lower limit of quantitation of the bioanalytical method; therefore no results are reported.

Notes: