



Clinical trial results:

An Open-label Extension of Study HGT-HIT-045 Evaluating Long-term Safety and Clinical Outcomes of Intrathecal Idursulfase-IT Administered in Conjunction With Intravenous ELAPRASE® in Pediatric Patients With Hunter Syndrome and Cognitive Impairment

Summary

EudraCT number	2011-000212-25
Trial protocol	GB Outside EU/EEA
Global end of trial date	30 April 2024

Results information

Result version number	v2 (current)
This version publication date	14 September 2025
First version publication date	13 November 2024
Version creation reason	<ul style="list-style-type: none">New data added to full data set New data added

Trial information

Trial identification

Sponsor protocol code	HGT-HIT-046
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01506141
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire Human Genetic Therapies (HGT), Inc.
Sponsor organisation address	300 Shire Way, Lexington, MA, United States, 02421
Public contact	Study Director, Takeda, TrialDisclosures@takeda.com
Scientific contact	Study Director, Takeda, TrialDisclosures@takeda.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000194-PIP20-13
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	30 April 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 April 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose was to collect long-term safety data in pediatric patients with Hunter syndrome and cognitive impairment who are receiving intrathecal idursulfase-IT and intravenous (IV) Elaprase® enzyme replacement therapy (ERT).

Protection of trial subjects:

All study participants or their guardians were required to read and sign an Informed Consent Form (ICF).

Background therapy:

NA

Evidence for comparator: -

Actual start date of recruitment	01 August 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 10
Country: Number of subjects enrolled	United Kingdom: 5
Worldwide total number of subjects	15
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	14
Adolescents (12-17 years)	1
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0
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Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at various investigative sites in the United States (US) and the United Kingdom (UK) from 01 August 2010 to 30 April 2024.

Pre-assignment

Screening details:

15 subjects who completed the StudyHGT-HIT-045(045) received idursulfase-IT+Elaprase therapy. Subjects who received idursulfase-IT treatment in 045, initiated treatment at same dose level & were analyzed as per reference timepoints of 045 for some evaluations. For others, reference timepoints after enrollment to this extension study were considered.

Period 1

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

Arms

Arm title	Idursulfase-IT
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Arm description:

Participants received either 10 or 30 milligrams (mg) idursulfase-IT intrathecally via intrathecal drug delivery device (IDDD) or lumbar puncture (LP) once monthly and standard-of-care (SoC) therapy of elaprase IV infusions up to a maximum of 157.2 months.

Arm type	Experimental
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 157.2 months.

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 once every 28 days for 157.2 months.

Number of subjects in period 1	Idursulfase-IT
Started	15
Completed	3
Not completed	12
Adverse event, non-fatal	2
Reason Not Specified	6
Site Terminated by Sponsor	2

Participation Terminated by Investigator	2
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Baseline characteristics

Reporting groups

Reporting group title	Idursulfase-IT
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Reporting group description:

Participants received either 10 or 30 milligrams (mg) idursulfase-IT intrathecally via intrathecal drug delivery device (IDDD) or lumbar puncture (LP) once monthly and standard-of-care (SoC) therapy of elaprase IV infusions up to a maximum of 157.2 months.

Reporting group values	Idursulfase-IT	Total	
Number of subjects	15	15	
Age Categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	6.41 ± 2.502	-	
Gender categorical Units: Subjects			
Male	15	15	
Female	0	0	
Race Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	1	1	
Black or African American	0	0	
Native Hawaiian or other Pacific Islander	0	0	
White	10	10	
Other	4	4	
Ethnicity Units: Subjects			
Hispanic or Latino	1	1	
Not Hispanic or Latino	12	12	
Not Reported	2	2	
Unknown	0	0	

Subject analysis sets

Subject analysis set title	Elaprase IV Infusion 0.5 mg/kg
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Participants received 0.5 mg/kg SoC therapy of elaprase IV infusions for up to a maximum of 157.2 months.

Subject analysis set title	Idursulfase-IT 1 mg
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Participants received 1 mg idursulfase-IT intrathecally via IDDD or LP once monthly and SoC therapy of Elaprase IV infusions for up to a maximum of 10.1 months.

Subject analysis set title	Idursulfase-IT 10 mg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received 10 mg idursulfase-IT initially intrathecally via IDDD or LP once monthly and SoC therapy of Elaprase IV infusions for up to a maximum of 157.2 months.	
Subject analysis set title	Idursulfase-IT 10 mg Comprehensive
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received 10 mg idursulfase-IT intrathecally via IDDD or LP once monthly and SoC therapy of elaprase IV infusions for up to a maximum of 157.2 months. This comprehensive group includes participants who received 10 mg idursulfase-IT at any point in the study.	
Subject analysis set title	Idursulfase-IT 30 mg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received 30 mg idursulfase-IT intrathecally via IDDD or LP once monthly and SoC therapy of Elaprase IV infusions for up to a maximum of 148.2 months.	

Reporting group values	Elaprase IV Infusion 0.5 mg/kg	Idursulfase-IT 1 mg	Idursulfase-IT 10 mg
Number of subjects	15	4	6
Age Categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean		5.61	5.68
standard deviation	±	± 1.799	± 2.501
Gender categorical			
Units: Subjects			
Male		4	6
Female		0	0
Race			
Units: Subjects			
American Indian or Alaska Native		0	0
Asian		0	0
Black or African American		0	0
Native Hawaiian or other Pacific Islander		0	0
White		2	4
Other		2	2
Ethnicity			
Units: Subjects			
Hispanic or Latino		0	1
Not Hispanic or Latino		4	4
Not Reported		0	1
Unknown		0	0

Reporting group values	Idursulfase-IT 10 mg Comprehensive	Idursulfase-IT 30 mg	
Number of subjects	10	5	
Age Categorical			
Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation		7.94 ± 2.706	
Gender categorical Units: Subjects			
Male		5	
Female		0	
Race Units: Subjects			
American Indian or Alaska Native		0	
Asian		1	
Black or African American		0	
Native Hawaiian or other Pacific Islander		0	
White		4	
Other		0	
Ethnicity Units: Subjects			
Hispanic or Latino		0	
Not Hispanic or Latino		4	
Not Reported		1	
Unknown		0	

End points

End points reporting groups

Reporting group title	Idursulfase-IT
Reporting group description: Participants received either 10 or 30 milligrams (mg) idursulfase-IT intrathecally via intrathecal drug delivery device (IDDD) or lumbar puncture (LP) once monthly and standard-of-care (SoC) therapy of elaprase IV infusions up to a maximum of 157.2 months.	
Subject analysis set title	Elaprase IV Infusion 0.5 mg/kg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants received 0.5 mg/kg SoC therapy of elaprase IV infusions for up to a maximum of 157.2 months.	
Subject analysis set title	Idursulfase-IT 1 mg
Subject analysis set type	Safety analysis
Subject analysis set description: Participants received 1 mg idursulfase-IT intrathecally via IDDD or LP once monthly and SoC therapy of Elaprase IV infusions for up to a maximum of 10.1 months.	
Subject analysis set title	Idursulfase-IT 10 mg
Subject analysis set type	Safety analysis
Subject analysis set description: Participants received 10 mg idursulfase-IT initially intrathecally via IDDD or LP once monthly and SoC therapy of Elaprase IV infusions for up to a maximum of 157.2 months.	
Subject analysis set title	Idursulfase-IT 10 mg Comprehensive
Subject analysis set type	Safety analysis
Subject analysis set description: Participants received 10 mg idursulfase-IT intrathecally via IDDD or LP once monthly and SoC therapy of elaprase IV infusions for up to a maximum of 157.2 months. This comprehensive group includes participants who received 10 mg idursulfase-IT at any point in the study.	
Subject analysis set title	Idursulfase-IT 30 mg
Subject analysis set type	Safety analysis
Subject analysis set description: Participants received 30 mg idursulfase-IT intrathecally via IDDD or LP once monthly and SoC therapy of Elaprase IV infusions for up to a maximum of 148.2 months.	

Primary: Number of Participants With Clinically Significant Changes or Apparent Difference Across Treatment Groups in 12-lead Electrocardiogram (ECG) Findings

End point title	Number of Participants With Clinically Significant Changes or Apparent Difference Across Treatment Groups in 12-lead Electrocardiogram (ECG) Findings ^[1]
End point description: Number of participants with clinically significant changes in laboratory parameters (chemistry, hematology, urinalysis and CSF values), and 12-lead Electrocardiogram (ECG) findings (heart rate, PR interval, QRS interval, QT interval and the corrected QT interval) were collected. Safety Population included all eligible participants from HGT-HIT-045 who had agreed to participate in the extension study and had either surgical implantation of an IDDD or intrathecal administration of study drug in the extension study.	
End point type	Primary
End point timeframe: From start of study drug administration up to follow-up (up to 165 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: Only descriptive analyses were planned for this outcome measure.

End point values	Idursulfase-IT 1 mg	Idursulfase-IT 10 mg Comprehensive	Idursulfase-IT 30 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	4	10	5	
Units: participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Treatment-emergent Adverse Events (TEAEs)

End point title	Number of Participants With Treatment-emergent Adverse Events (TEAEs) ^[2]
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End point description:

An adverse event (AE) is any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, and/or laboratory changes occurring in any phase of a clinical trial, and whether or not considered study drug-related. TEAEs were defined as all AEs occurring on or after the first IDDD surgery date or first dose (whichever is earlier) for the participant (whether it is in this extension study or in HGT HIT-045 [NCT00920647]) and before the end of the study (EOS) visit (+30 days). Safety Population included all eligible participants from HGT-HIT-045 who had agreed to participate in the extension study and had either surgical implantation of an IDDD or intrathecal administration of study drug in the extension study.

End point type	Primary
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End point timeframe:

From start of study drug administration up to follow-up (up to 165 months)

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 analyses were planned for this outcome measure.

End point values	Idursulfase-IT 1 mg	Idursulfase-IT 10 mg Comprehensive	Idursulfase-IT 30 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	4	10	5	
Units: participants	4	10	5	

Statistical analyses

No statistical analyses for this end point

Primary: CSF Chemistries: Change from Baseline in CSF Glucose

End point title	CSF Chemistries: Change from Baseline in CSF Glucose ^[3]
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End point description:

Safety Population included all eligible participants from HGT-HIT-045 who had agreed to participate in the extension study and had either surgical implantation of an IDDD or intrathecal administration of study drug in the extension study. Subjects analysed are the number of participants who had data at Baseline. 'n' indicates the number of participants with data available for analyses at specified time points. 999 indicates no data values were reported as 0 participants were available for analyses at the specified time point.

End point type	Primary
End point timeframe:	
Baseline, Month 163	
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 analyses were planned for this outcome measure.	

End point values	Idursulfase-IT 1 mg	Idursulfase-IT 10 mg	Idursulfase-IT 30 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	4	6	5	
Units: millimoles per litre (mmol/L)				
arithmetic mean (standard deviation)				
Baseline (BL) (n=4,6,5)	2.950 (± 0.265)	2.850 (± 0.217)	3.000 (± 0.200)	
Change from BL in CSF Glucose at Month163(n=0,3,0)	999 (± 999)	0.523 (± 0.436)	999 (± 999)	

Statistical analyses

No statistical analyses for this end point

Primary: CSF Chemistries: Change from Baseline in Cerebrospinal Fluid (CSF) Total Cell Count

End point title	CSF Chemistries: Change from Baseline in Cerebrospinal Fluid (CSF) Total Cell Count ^[4]
End point description:	
Safety Population included all eligible participants from HGT-HIT-045 who had agreed to participate in the extension study and had either surgical implantation of an IDDD or intrathecal administration of study drug in the extension study. Subjects analysed are the number of participants who had data at Baseline. 'n' indicates the number of participants with data available for analyses at specified time points. Total Cell Count is indicated as TCC. 999 indicates no data values were reported as 0 participants were available for analyses at the specified time point.	
End point type	Primary
End point timeframe:	
Baseline, Month 163	
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 analyses were planned for this outcome measure.	

End point values	Idursulfase-IT 1 mg	Idursulfase-IT 10 mg	Idursulfase-IT 30 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	4	6	5	
Units: 10 ⁶ /litre (L)				
arithmetic mean (standard deviation)				
BL (n=4,6,5)	1.0 (± 0.00)	1.0 (± 0.00)	1.0 (± 0.00)	
Change From BL in CSF TCC at Month163 (n=0,3,0)	999 (± 999)	7.3 (± 11.85)	999 (± 999)	

Statistical analyses

No statistical analyses for this end point

Primary: CSF Chemistries: Change from Baseline in CSF Protein

End point title	CSF Chemistries: Change from Baseline in CSF Protein ^[5]
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End point description:

Safety Population included all eligible participants from HGT-HIT-045 who had agreed to participate in the extension study and had either surgical implantation of an IDDD or intrathecal administration of study drug in the extension study. Subjects analysed are the number of participants who had data at Baseline. 'n' indicates the number of participants with data available for analyses at specified time points. 999 indicates no data values are reported as 0 participants were available for analyses at the specified time point.

End point type	Primary
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End point timeframe:

Baseline, Month 163

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 analyses were planned for this outcome measure.

End point values	Idursulfase-IT 1 mg	Idursulfase-IT 10 mg	Idursulfase-IT 30 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	4	6	5	
Units: grams per litre (g/L)				
arithmetic mean (standard deviation)				
BL (n=4,6,5)	0.400 (± 0.194)	0.282 (± 0.144)	0.530 (± 0.368)	
Change from BL in CSF Protein at Month163(n=0,3,0)	999 (± 999)	0.493 (± 0.229)	999 (± 999)	

Statistical analyses

No statistical analyses for this end point

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

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

Safety Population included all eligible participants from HGT-HIT-045 who had agreed to participate in the extension study and had either surgical implantation of an IDDD or intrathecal administration of study drug in the extension study. 'n' indicates the number of participants with data available for analyses at specified time points.

End point type	Primary
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End point timeframe:

From start of study drug administration up to follow-up (up to 165 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: Only descriptive analyses were planned for this outcome measure.

End point values	Idursulfase-IT 1 mg	Idursulfase-IT 10 mg Comprehensive	Idursulfase-IT 30 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	4	10	5	
Units: participants				
At BL (n=4,6,5)	3	1	1	
Post-BL (n=4,10,5)	3	5	1	

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Participants who Reported Anti-idursulfase Antibodies in Serum ^[7]
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End point description:

Safety Population included all eligible participants from HGT-HIT-045 who had agreed to participate in the extension study and had either surgical implantation of an IDDD or intrathecal administration of study drug in the extension study. 'n' indicates the number of participants with data available for analyses at specified time points.

End point type	Primary
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End point timeframe:

From start of study drug administration up to follow-up (up to 165 months)

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 analyses were planned for this outcome measure.

End point values	Idursulfase-IT 1 mg	Idursulfase-IT 10 mg Comprehensive	Idursulfase-IT 30 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	4	10	5	
Units: participants				
At BL (n=4,6,5)	3	2	2	
Post-BL (n=4,10,5)	3	6	3	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Clinically Significant Changes or Apparent

Difference Across Treatment Groups in Laboratory Parameters

End point title	Number of Participants With Clinically Significant Changes or Apparent Difference Across Treatment Groups in Laboratory Parameters ^[8]
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End point description:

Number of participants with clinically significant changes in laboratory parameters (chemistry, hematology, urinalysis and CSF values) were collected. Safety Population included all eligible participants from HGT-HIT-045 who had agreed to participate in the extension study and had either surgical implantation of an IDDD or intrathecal administration of study drug in the extension study.

End point type	Primary
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End point timeframe:

From start of study drug administration up to follow-up (up to 165 months)

Notes:

[8] - 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 analyses were planned for this outcome measure.

End point values	Idursulfase-IT 1 mg	Idursulfase-IT 10 mg Comprehensive	Idursulfase-IT 30 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	4	10	5	
Units: participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve Extrapolated to Infinity (AUC₀-infinity) of Idursulfase Administered as Intrathecal and in Conjunction With Elaprase

End point title	Area Under the Curve Extrapolated to Infinity (AUC ₀ -infinity) of Idursulfase Administered as Intrathecal and in Conjunction With Elaprase
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End point description:

AUC₀-infinity, calculated using the observed value of the last non-zero concentration (AUC₀-infinity) of idursulfase was assessed. Participants in 1 mg arm group were assessed for Pharmacokinetic (PK) analysis in the HGT-HIT-045 study. PK population included all participants who received study drug and participated in the scheduled pharmacokinetic studies, and for whom at least 1 post-dose PK blood sample was collected. Subjects analysed indicates the number of participants with data available for analyses. 'n' indicates the number of participants with data available for analysis for the specified category. 999 indicates that there were 0 participants with data available for analyses at the specified timepoint. 9999 indicates Mean and Standard Deviation (SD) were not estimable as values were below lower limit of quantification (LLOQ) and 99999 indicates SD was not estimable for a single participant.

End point type	Secondary
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End point timeframe:

15 minutes prior to IT injection, at 1,2,3,4,6,8,12,24,30,36 hours (±1 hour) following IT injection on Day 2 of Weeks 3,23, for 1 mg arm group and on Day 2 of Weeks 3,23, Months 19,31,43,55,67,79 for 10 and 30 mg arm groups

End point values	Idursulfase-IT 1 mg	Idursulfase-IT 10 mg	Idursulfase-IT 30 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	6	5	
Units: hours*nanograms per millilitre (h*ng/mL)				
arithmetic mean (standard deviation)				
Week 3: Day 2 (n=3,0,0)	9999 (± 9999)	999 (± 999)	999 (± 999)	
Week 23: Day 2 (n=1,1,0)	1574.37 (± 99999)	1765 (± 99999)	999 (± 999)	
Month 19: Day 2 (n=0,3,2)	999 (± 999)	2869 (± 563.1)	5179 (± 2579.8)	
Month 31: Day 2 (n=0,6,1)	999 (± 999)	2649 (± 1334.8)	4766 (± 99999)	
Month 43 (n=0,4,2)	999 (± 999)	2324 (± 203.0)	4395 (± 733.1)	
Month 55 (n=0,3,2)	999 (± 999)	1636 (± 351.4)	2445 (± 1770.8)	
Month 67 (n=0,2,2)	999 (± 999)	1649 (± 167.4)	3270 (± 801.6)	
Month 79 (n=0,3,0)	999 (± 999)	1865 (± 775.2)	999 (± 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve From the Time of Dosing to the Last Measurable Concentration (AUC0-t) of Idursulfase Administered as Intrathecal and in Conjunction With Elaprase

End point title	Area Under the Curve From the Time of Dosing to the Last Measurable Concentration (AUC0-t) of Idursulfase Administered as Intrathecal and in Conjunction With Elaprase
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End point description:

PK population included all participants who received study drug and participated in the scheduled pharmacokinetic studies, and for whom at least 1 post-dose PK blood sample was collected. Participants in 1 mg arm group were assessed for PK analysis in the HGT-HIT-045 study. Number of subjects analysed indicates the number of participants with data available for analyses. 'n' indicates the number of participants with data available for analysis for the specified category. 999 indicates that there were 0 participants with data available for analyses at the specified timepoint. 9999 indicates mean and SD were not estimable as values were below LLOQ and 99999 indicates SD was not estimable for a single participant.

End point type	Secondary
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End point timeframe:

15 minutes prior to IT injection, at 1,2,3,4,6,8,12,24,30,36 hours (±1 hour) following IT injection on Day 2 of Weeks 3,23, for 1 mg arm group and on Day 2 of Weeks 3,23, Months 19,31,43,55,67,79 for 10 and 30 mg arm groups

End point values	Idursulfase-IT 1 mg	Idursulfase-IT 10 mg Comprehensive	Idursulfase-IT 30 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	7	5	
Units: h*ng/mL				
arithmetic mean (standard deviation)				

Week 3: Day 2 (n=3,1,1)	9999 (± 9999)	1214 (± 99999)	3746 (± 99999)	
Week 23: Day 2 (n=1,1,1)	524.68 (± 99999)	1047 (± 99999)	4855 (± 99999)	
Month 19: Day 2 (n=0,7,5)	999 (± 999)	1633 (± 976.6)	3525 (± 835.5)	
Month 31: Day 2 (n=0,6,4)	999 (± 999)	2031 (± 1081.9)	3586 (± 1056.9)	
Month 43 (n=0,4,4)	999 (± 999)	1944 (± 295.8)	3141 (± 979.7)	
Month 55 (n=0,6,3)	999 (± 999)	1356 (± 235.3)	1466 (± 1511.8)	
Month 67 (n=0,3,3)	999 (± 999)	1247 (± 204.0)	2415 (± 394.8)	
Month 79 (n=0,4,0)	999 (± 999)	1500 (± 347.1)	999 (± 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Concentration (Cmax) of Idursulfase Administered as Intrathecal and in Conjunction With Elaprase

End point title	Maximum Observed Concentration (Cmax) of Idursulfase Administered as Intrathecal and in Conjunction With Elaprase
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End point description:

PK population included all participants who received study drug and participated in the scheduled pharmacokinetic studies, and for whom at least 1 post-dose PK blood sample was collected. Participants in 1 mg arm group were assessed for PK analysis in the HGT-HIT-045 study. Number of subjects analysed indicates the number of participants with data available for analyses. 'n' indicates the number of participants with data available for analysis for the specified category. 999 indicates that there were 0 participants with data available for analyses at the specified timepoint. 9999 indicates mean and SD were not estimable as values were below LLOQ and 99999 indicates SD was not estimable for a single participant.

End point type	Secondary
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End point timeframe:

15 minutes prior to IT injection, at 1,2,3,4,6,8,12,24,30,36 hours (±1 hour) following IT injection on Day 2 of Weeks 3,23, for 1 mg arm group and on Day 2 of Weeks 3,23, Months 19,31,43,55,67,79 for 10 and 30 mg arm groups

End point values	Idursulfase-IT 1 mg	Idursulfase-IT 10 mg Comprehensive	Idursulfase-IT 30 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	7	5	
Units: nanograms per millilitre (ng/mL)				
arithmetic mean (standard deviation)				
Week 3: Day 2 (n=3,1,1)	9999 (± 9999)	43.95 (± 99999)	146.75 (± 99999)	
Week 23: Day 2 (n=1,1,1)	19 (± 99999)	36.10 (± 99999)	173.40 (± 99999)	
Month 19: Day 2 (n=0,7,5)	999 (± 999)	76.39 (± 51.386)	156.80 (± 33.054)	
Month 31: Day 2 (n=0,6,4)	999 (± 999)	143.52 (± 122.774)	175.20 (± 70.083)	
Month 43 (n=0,4,4)	999 (± 999)	90.57 (± 28.720)	144.35 (± 44.434)	

Month 55 (n=0,6,3)	999 (± 999)	61.50 (± 19.330)	93.43 (± 61.406)	
Month 67 (n=0,3,3)	999 (± 999)	56.73 (± 12.690)	99.20 (± 19.762)	
Month 79 (n=0,4,0)	999 (± 999)	64.08 (± 7.835)	999 (± 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time of Maximum Observed Concentration (tmax) of Idursulfase Administered in as Intrathecal and in Conjunction With Elaprase

End point title	Time of Maximum Observed Concentration (tmax) of Idursulfase Administered in as Intrathecal and in Conjunction With Elaprase
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End point description:

PK population included all participants who received study drug and participated in the scheduled pharmacokinetic studies, and for whom at least 1 post-dose PK blood sample was collected. Participants in 1 mg arm group were assessed for PK analysis in the HGT-HIT-045 study. Number of subjects analysed indicates the number of participants with data available for analyses. 'n' indicates the number of participants with data available for analysis for the specified category. 999 indicates that there were 0 participants with data available for analyses at the specified timepoint. 9999 indicates median and full range were not estimable as values were below LLOQ and 0.99999 to 99999 indicates full range was not estimable for a single participant.

End point type	Secondary
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End point timeframe:

15 minutes prior to IT injection, at 1,2,3,4,6,8,12,24,30,36 hours (±1 hour) following IT injection on Day 2 of Weeks 3,23, for 1 mg arm group and on Day 2 of Weeks 3,23, Months 19,31,43,55,67,79 for 10 and 30 mg arm groups

End point values	Idursulfase-IT 1 mg	Idursulfase-IT 10 mg Comprehensive	Idursulfase-IT 30 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	7	5	
Units: hours				
median (full range (min-max))				
Week 3: Day 2 (n=3,1,1)	9999 (9999 to 9999)	24.03 (0.99999 to 99999)	36.07 (0.99999 to 99999)	
Week 23: Day 2 (n=1,1,1)	8.03 (0.99999 to 99999)	12.00 (0.99999 to 99999)	12.00 (0.99999 to 99999)	
Month 19: Day 2 (n=0,7,5)	999 (999 to 999)	12.00 (6.00 to 36.2)	24.00 (2.00 to 30.0)	
Month 31: Day 2 (n=0,6,4)	999 (999 to 999)	9.99 (1.12 to 12.0)	17.98 (6.00 to 30.1)	
Month 43 (n=0,4,4)	999 (999 to 999)	12.00 (8.00 to 12.0)	10.02 (6.03 to 12.0)	
Month 55 (n=0,6,3)	999 (999 to 999)	12.00 (6.00 to 12.0)	7.97 (2.00 to 8.00)	
Month 67 (n=0,3,3)	999 (999 to 999)	12.00 (6.00 to 12.0)	12.00 (6.00 to 30.0)	

Month 79 (n=0,4,0)	999 (999 to 999)	10.00 (8.00 to 12.00)	999 (999 to 999)	
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Statistical analyses

No statistical analyses for this end point

Secondary: Total Body Clearance for Extravascular Administration Divided by the Fraction of Dose Absorbed (CL/F) of Idursulfase-IT Administered as Intrathecal and in Conjunction With Elaprase

End point title	Total Body Clearance for Extravascular Administration Divided by the Fraction of Dose Absorbed (CL/F) of Idursulfase-IT Administered as Intrathecal and in Conjunction With Elaprase
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End point description:

PK population included all participants who received study drug and participated in the scheduled pharmacokinetic studies, and for whom at least 1 post-dose PK blood sample was collected. Participants in 1 mg arm group were assessed for PK analysis in the HGT-HIT-045 study. Number of subjects analysed indicates the number of participants with data available for analyses. 'n' indicates the number of participants with data available for analysis for the specified category. 999 indicates that there were 0 participants with data available for analyses at the specified timepoint. 9999 indicates mean and SD were not estimable as values were below LLOQ and 99999 indicates SD was not estimable for a single participant.

End point type	Secondary
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End point timeframe:

15 minutes prior to IT injection, at 1,2,3,4,6,8,12,24,30,36 hours (± 1 hour) following IT injection on Day 2 of Weeks 3,23, for 1 mg arm group and on Day 2 of Weeks 3,23, Months 19,31,43,55,67,79 for 10 and 30 mg arm groups

End point values	Idursulfase-IT 1 mg	Idursulfase-IT 10 mg	Idursulfase-IT 30 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	6	5	
Units: litres per hour (L/h)				
arithmetic mean (standard deviation)				
Week 3: Day 2 (n=3,0,0)	9999 (\pm 9999)	999 (\pm 999)	999 (\pm 999)	
Week 23: Day 2 (n=2,1,0)	9999 (\pm 9999)	5.67 (\pm 99999)	999 (\pm 999)	
Month 19: Day 2 (n=0,3,2)	999 (\pm 999)	3.59 (\pm 0.763)	6.61 (\pm 3.295)	
Month 31: Day 2 (n=0,6,1)	999 (\pm 999)	4.80 (\pm 2.667)	6.29 (\pm 99999)	
Month 43 (n=0,4,2)	999 (\pm 999)	4.33 (\pm 0.377)	6.92 (\pm 1.154)	
Month 55 (n=0,3,2)	999 (\pm 999)	6.33 (\pm 1.548)	8.25 (\pm 0.191)	
Month 67 (n=0,2,2)	999 (\pm 999)	6.10 (\pm 0.619)	9.46 (\pm 2.319)	
Month 79 (n=0,3,0)	999 (\pm 999)	5.96 (\pm 2.207)	999 (\pm 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution Associated With the Terminal Slope Following Extravascular Administration Divided by the Fraction of Dose Absorbed (V_z/F) of Idursulfase Administered as Intrathecal and in Conjunction With Elaprase

End point title	Volume of Distribution Associated With the Terminal Slope Following Extravascular Administration Divided by the Fraction of Dose Absorbed (V _z /F) of Idursulfase Administered as Intrathecal and in Conjunction With Elaprase
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End point description:

PK population included all participants who received study drug and participated in the scheduled pharmacokinetic studies, and for whom at least 1 post-dose PK blood sample was collected. Participants in 1 mg arm group were assessed for PK analysis in the HGT-HIT-045 study. Number of subjects analysed indicates the number of participants with data available for analyses. 'n' indicates the number of participants with data available for analysis for the specified category. 999 indicates that there were 0 participants with data available for analyses at the specified timepoint. 9999 indicates mean and SD were not estimable as values were below LLOQ and 99999 indicates SD was not estimable for a single participant.

End point type	Secondary
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End point timeframe:

15 minutes prior to IT injection, at 1,2,3,4,6,8,12,24,30,36 hours (±1 hour) following IT injection on Day 2 of Weeks 3,23, for 1 mg arm group and on Day 2 of Weeks 3,23, Months 19,31,43,55,67,79 for 10 and 30 mg arm groups

End point values	Idursulfase-IT 1 mg	Idursulfase-IT 10 mg	Idursulfase-IT 30 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	6	5	
Units: litres				
arithmetic mean (standard deviation)				
Week 3: Day 2 (n=3,0,0)	9999 (± 9999)	999 (± 999)	999 (± 999)	
Week 23: Day 2 (n=1,1,0)	52.831 (± 99999)	183.31 (± 99999)	999 (± 999)	
Month 19: Day 2 (n=0,3,2)	999 (± 999)	94.18 (± 21.961)	152.82 (± 45.153)	
Month 31: Day 2 (n=0,6,1)	999 (± 999)	116.91 (± 84.881)	128.63 (± 99999)	
Month 43 (n=0,4,2)	999 (± 999)	68.06 (± 21.783)	104.93 (± 44.848)	
Month 55 (n=0,3,2)	999 (± 999)	130.84 (± 15.624)	127.77 (± 11.009)	
Month 67 (n=0,2,2)	999 (± 999)	115.31 (± 29.260)	206.92 (± 11.864)	
Month 79 (n=0,3,0)	999 (± 999)	79.22 (± 8.364)	999 (± 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: First Order Rate Constant (Lambda z) of Idursulfase Administered as Intrathecal and in Conjunction With Elaprase

End point title	First Order Rate Constant (Lambda z) of Idursulfase Administered as Intrathecal and in Conjunction With Elaprase
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End point description:

PK population included all participants who received study drug and participated in the scheduled pharmacokinetic studies, and for whom at least 1 post-dose PK blood sample was collected. Participants in 1 mg arm group were assessed for PK analysis in the HGT-HIT-045 study. Number of subjects analysed indicates the number of participants with data available for analyses. 'n' indicates the number of participants with data available for analysis for the specified category. 999 indicates that there were 0 participants with data available for analyses at the specified timepoint. 9999 indicates mean and SD were not estimable as values were below LLOQ and 99999 indicates SD was not estimable for a single participant.

End point type	Secondary
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End point timeframe:

15 minutes prior to IT injection, at 1,2,3,4,6,8,12,24,30,36 hours (± 1 hour) following IT injection on Day 2 of Weeks 3,23, for 1 mg arm group and on Day 2 of Weeks 3,23, Months 19,31,43,55,67,79 for 10 and 30 mg arm groups

End point values	Idursulfase-IT 1 mg	Idursulfase-IT 10 mg	Idursulfase-IT 30 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	6	5	
Units: per hour (/h)				
arithmetic mean (standard deviation)				
Week 3: Day 2 (n=3,0,0)	9999 (\pm 9999)	999 (\pm 999)	999 (\pm 999)	
Week 23: Day 2 (n=2,1,0)	9999 (\pm 9999)	0.0309 (\pm 99999)	999 (\pm 999)	
Month 19: Day 2 (n=0,3,2)	999 (\pm 999)	0.0383 (\pm 0.00260)	0.0419 (\pm 0.00917)	
Month 31: Day 2 (n=0,6,1)	999 (\pm 999)	0.0487 (\pm 0.01996)	0.0489 (\pm 99999)	
Month 43 (n=0,4,2)	999 (\pm 999)	0.0677 (\pm 0.01829)	0.0700 (\pm 0.01892)	
Month 55 (n=0,3,2)	999 (\pm 999)	0.0486 (\pm 0.01126)	0.0649 (\pm 0.00708)	
Month 67 (n=0,2,2)	999 (\pm 999)	0.0539 (\pm 0.00831)	0.0455 (\pm 0.00860)	
Month 79 (n=0,3,0)	999 (\pm 999)	0.0772 (\pm 0.03550)	999 (\pm 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Half-life ($t_{1/2}$) of Idursulfase Administered as Intrathecal and in Conjunction With Elaprase

End point title	Terminal Half-life ($t_{1/2}$) of Idursulfase Administered as Intrathecal and in Conjunction With Elaprase
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End point description:

Participants in 1 mg arm group were assessed for PK analysis in the HGT-HIT-045 study. $T_{1/2}$ is calculated by dividing 0.693 by Lambda z. Here, 0.693 is the natural logarithm of 2 and Lambda z is the first order rate constant. PK population included all participants who received study drug and participated in the scheduled pharmacokinetic studies, and for whom at least 1 post-dose PK blood sample was collected. Number of subjects analysed indicates the number of participants with data available for analyses. 'n' indicates the number of participants with data available for analysis for the specified category. 999 indicates that there were 0 participants with data available for analyses at the specified timepoint. 9999=median and Full range were not estimable as values were below LLOQ;

99999= $t_{1/2}$ was not estimable due to non-availability of the Lambda z values and 0.999999 to 999999=full range was not estimable for a single participant.

End point type	Secondary
End point timeframe:	
15 minutes prior to IT injection, at 1,2,3,4,6,8,12,24,30,36 hours (± 1 hour) following IT injection on Day 2 of Weeks 3,23, for 1 mg arm group and on Day 2 of Weeks 3,23, Months 19,31,43,55,67,79 for 10 and 30 mg arm groups	

End point values	Idursulfase-IT 1 mg	Idursulfase-IT 10 mg	Idursulfase-IT 30 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	6	5	
Units: hours				
median (full range (min-max))				
Week 3: Day 2 (n=3,0,0)	9999 (9999 to 9999)	999 (999 to 999)	999 (999 to 999)	
Week 23: Day 2 (n=1,1,0)	99999 (99999 to 99999)	22.43 (0.999999 to 999999)	999 (999 to 999)	
Month 19: Day 2 (n=0,3,2)	999 (999 to 999)	18.20 (16.9 to 19.4)	16.94 (14.3 to 19.6)	
Month 31: Day 2 (n=0,6,1)	999 (999 to 999)	15.57 (8.35 to 29.8)	14.16 (0.999999 to 999999)	
Month 43 (n=0,4,2)	999 (999 to 999)	10.28 (8.21 to 14.7)	10.28 (8.31 to 12.2)	
Month 55 (n=0,3,2)	999 (999 to 999)	14.21 (11.6 to 18.6)	10.75 (9.92 to 11.6)	
Month 67 (n=0,2,2)	999 (999 to 999)	13.01 (11.6 to 14.4)	15.52 (13.4 to 17.6)	
Month 79 (n=0,3,0)	999 (999 to 999)	9.68 (6.02 to 15.4)	999 (999 to 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution (V_z) of Elaprase

End point title	Volume of Distribution (V _z) of Elaprase
End point description:	
PK population included all participants who received study drug and participated in the scheduled pharmacokinetic studies, and for whom at least 1 post-dose PK blood sample was collected. Participants who received only Elaprase in HGT-HIT-045 and had evaluable samples were analyzed for this outcome measure. Number of subjects analysed indicates the number of participants with data available for analyses. 'n' indicates the number of participants with data available for analysis for the specified category. 9999 indicates that standard deviation was not estimable for a single participant.	
End point type	Secondary
End point timeframe:	
15 minutes prior to IV infusion and at multiple timepoints (0.5, 1, 1.5, 2, 2.5, and 3 hours during the infusion; and at 3.5, 4, 5, 6, 7, 9, 11, and 24 hours) following IV infusion on Days 3-7 of Weeks 3 and 23	

End point values	Elaprase IV Infusion 0.5 mg/kg			
Subject group type	Subject analysis set			
Number of subjects analysed	2			
Units: litres				
arithmetic mean (standard deviation)				
Week 3: Day 3-7 (n=2)	19.91 (± 13.874)			
Week 23: Day 3-7 (n=1)	34.20 (± 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total Body Clearance (CL) of Elaprase

End point title	Total Body Clearance (CL) of Elaprase
End point description:	
PK population included all participants who received study drug and participated in the scheduled pharmacokinetic studies, and for whom at least 1 post-dose PK blood sample was collected. Participants who received only Elaprase in HGT-HIT-045 and had evaluable samples were analyzed for this outcome measure. Number of subjects analysed indicates the number of participants with data available for analyses. 'n' indicates the number of participants with data available for analysis for the specified category. 9999 indicates that standard deviation was not estimable for a single participant.	
End point type	Secondary
End point timeframe:	
15 minutes prior to IV infusion, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 9, 11, and 24 hours during/after the IV infusion on Days 3-7 of Weeks 3 and 23	

End point values	Elaprase IV Infusion 0.5 mg/kg			
Subject group type	Subject analysis set			
Number of subjects analysed	2			
Units: L/h				
arithmetic mean (standard deviation)				
Week 3: Day 3-7 (n=2)	1.94 (± 1.677)			
Week 23: Day 3-7 (n=1)	3.47 (± 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Observed Steady-state Volume of Distribution (Vss) of Elaprase

End point title	Observed Steady-state Volume of Distribution (Vss) of Elaprase
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End point description:

PK population included all participants who received study drug and participated in the scheduled pharmacokinetic studies, and for whom at least 1 post-dose PK blood sample was collected. Participants who received only Elaprase in HGT-HIT-045 and had evaluable samples were analyzed for this outcome measure. Number of subjects analysed indicates the number of participants with data available for analyses. 'n' indicates the number of participants with data available for analysis for the specified category. 9999 indicates that standard deviation was not estimable for a single participant.

End point type	Secondary
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End point timeframe:

15 minutes prior to IV infusion and at multiple timepoint (0.5, 1, 1.5, 2, 2.5, and 3 hours during the infusion; and at 3.5, 4, 5, 6, 7, 9, 11, and 24 hours) following IV infusion on Days 3-7 of Weeks 3 and 23

End point values	Elaprase IV Infusion 0.5 mg/kg			
Subject group type	Subject analysis set			
Number of subjects analysed	2			
Units: litres				
arithmetic mean (standard deviation)				
Week 3: Day 3-7 (n=2)	9.40 (± 3.464)			
Week 23: Day 3-7 (n=1)	13.19 (± 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Residence Time Extrapolated to Infinity (MRT0-inf) of Elaprase

End point title	Mean Residence Time Extrapolated to Infinity (MRT0-inf) of Elaprase
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End point description:

PK population included all participants who received study drug and participated in the scheduled pharmacokinetic studies, and for whom at least 1 post-dose PK blood sample was collected. Participants who received only Elaprase in HGT-HIT-045 and had evaluable samples were analyzed for this outcome measure. Number of subjects analysed indicates the number of participants with data available for analyses. 'n' indicates the number of participants with data available for analysis for the specified category. 9999 indicates that standard deviation was not estimable for a single participant.

End point type	Secondary
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End point timeframe:

15 minutes prior to IV infusion and at multiple timepoints (0.5, 1, 1.5, 2, 2.5, and 3 hours during the infusion; and at 3.5, 4, 5, 6, 7, 9, 11, and 24 hours) following IV infusion on Days 3-7 of Weeks 3 and 23

End point values	Elaprase IV Infusion 0.5 mg/kg			
Subject group type	Subject analysis set			
Number of subjects analysed	2			
Units: hours				
arithmetic mean (standard deviation)				
Week 3: Day 3-7 (n=2)	6.49 (± 3.817)			
Week 23: Day 3-7 (n=1)	3.80 (± 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Cerebrospinal Fluid (CSF) Biomarkers

End point title	Change From Baseline in Cerebrospinal Fluid (CSF) Biomarkers
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End point description:

Change from baseline in CSF biomarkers glycosaminoglycan (GAG [heparan sulfate (HS)/dermatan sulfate (DS)]) was assessed. Safety Population included all eligible participants from HGT-HIT-045 who had agreed to participate in the extension study and have had either surgical implantation of an IDDD or intrathecal administration of study drug in the extension study. 'n' is the number of participants with data available for analyses. A few participants from the 1 mg arm had transitioned to 10 mg arm before the analysis at Month 7 was performed for this outcome measure. 999 indicates that there were 0 participants with data available for analyses at the specified timepoint. 9999 indicates SD was not estimable for a single participant.

End point type	Secondary
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End point timeframe:

Baseline, Months 7, 55, and 139

End point values	Idursulfase-IT 1 mg	Idursulfase-IT 10 mg Comprehensive	Idursulfase-IT 30 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	4	10	5	
Units: ng/mL				
arithmetic mean (standard deviation)				
BL (n=4,6,5)	1922.34 (± 1164.679)	1874.00 (± 979.459)	1111.92 (± 485.898)	
Change from BL at Month 7 (n=2,7,5)	-807.50 (± 569.461)	-1526.24 (± 638.893)	-987.65 (± 437.885)	
Change from BL at Month 55 (n=0,9,3)	999 (± 999)	-1575.63 (± 906.621)	-974.07 (± 558.075)	
Change from BL at Month 139 (n=0,4,1)	999 (± 999)	-1169.25 (± 530.781)	-1135.51 (± 9999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Urinary Glycosaminoglycan (GAG)

End point title	Change From Baseline in Urinary Glycosaminoglycan (GAG)
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End point description:

Change from baseline in urinary GAG was assessed. mg GAG/mmol creatinine stands for milligrams of GAG per millimole of creatinine. Safety Population included all eligible participants from HGT-HIT-045 who had agreed to participate in the extension study and have had either surgical implantation of an IDDD or intrathecal administration of study drug in the extension study. 999 indicates that there were 0 participants with data available for analysis at the specified timepoint.

End point type	Secondary
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End point timeframe:

Baseline, Months 7, 55, and 163

End point values	Idursulfase-IT 1 mg	Idursulfase-IT 10 mg Comprehensive	Idursulfase-IT 30 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	4	10	5	
Units: mg GAG/mmol creatinine				
arithmetic mean (standard deviation)				
BL (n=4,6,7)	34.07 (± 20.132)	23.35 (± 13.799)	13.67 (± 7.200)	
Change from BL at Month 7 (n=4,6,3)	5.22 (± 6.084)	-4.20 (± 4.278)	3.35 (± 1.324)	
Change from BL at Month 55 (n=0,7,3)	999 (± 999)	-6.83 (± 5.837)	6.33 (± 7.387)	
Change from BL at Month 163 (n=0,2,0)	999 (± 999)	-13.88 (± 5.163)	999 (± 999)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study drug administration up to follow-up (up to 165 months)

Adverse event reporting additional description:

Safety Population included all eligible participants from HGT-HIT-045 who had agreed to participate in the extension study and have had either surgical implantation of an IDDD or intrathecal administration of study drug in the extension study.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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Reporting groups

Reporting group title	Idursulfase-IT 1 mg
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Reporting group description:

Participants received 1 mg idursulfase-IT intrathecally via IDDD or LP once monthly and SoC therapy of elaprase IV infusions for up to a maximum of 10.1 months.

Reporting group title	Idursulfase-IT 30 mg
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Reporting group description:

Participants received 30 mg idursulfase-IT intrathecally via IDDD or LP once monthly and SoC therapy of elaprase IV infusions for up to a maximum of 148.2 months.

Reporting group title	Idursulfase-IT 10 mg Comprehensive
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Reporting group description:

Participants received 10 mg idursulfase-IT initially intrathecally via IDDD or LP once monthly and SoC therapy of Elaprase IV infusions up to a maximum of 157.2 months. This included participants who received 1 mg idursulfase-IT initially and then switched to receive 10 mg idursulfase-IT in this arm group after Month 7 or later. These participants were analyzed in this arm group since transition to this group.

Serious adverse events	Idursulfase-IT 1 mg	Idursulfase-IT 30 mg	Idursulfase-IT 10 mg Comprehensive
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 4 (75.00%)	4 / 5 (80.00%)	9 / 10 (90.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Pallor			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Device difficult to use			

subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device dislocation			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	4 / 10 (40.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device connection issue			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
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 breakage			
subjects affected / exposed	1 / 4 (25.00%)	1 / 5 (20.00%)	4 / 10 (40.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device failure			
subjects affected / exposed	0 / 4 (0.00%)	2 / 5 (40.00%)	5 / 10 (50.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device malfunction			
subjects affected / exposed	1 / 4 (25.00%)	2 / 5 (40.00%)	4 / 10 (40.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device occlusion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular complication associated with device			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	3 / 10 (30.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	3 / 10 (30.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Granuloma			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait disturbance			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (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
Reproductive system and breast disorders			
Testicular torsion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspiration			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenoidal hypertrophy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Acute respiratory distress syndrome			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchospasm			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (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
Respiratory failure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngospasm			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			

CSF white blood cell count increased subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (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
Injury, poisoning and procedural complications			
Feeding tube complication subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheostomy malfunction subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound dehiscence subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound haematoma subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Tachycardia subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (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
Nervous system disorders			
Convulsion subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	3 / 10 (30.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atonic seizures			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrospinal fluid leakage			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	2 / 10 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure like phenomena			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lethargy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 4 (25.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Swollen tongue			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Petechiae			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (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
Musculoskeletal and connective tissue disorders			
Resorption bone increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (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
Back pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations Bacteraemia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 4 (0.00%) 0 / 0 0 / 0	0 / 5 (0.00%) 0 / 0 0 / 0	1 / 10 (10.00%) 0 / 2 0 / 0
Appendicitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 4 (0.00%) 0 / 0 0 / 0	0 / 5 (0.00%) 0 / 0 0 / 0	1 / 10 (10.00%) 0 / 1 0 / 0
Adenovirus infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 4 (0.00%) 0 / 0 0 / 0	0 / 5 (0.00%) 0 / 0 0 / 0	1 / 10 (10.00%) 0 / 1 0 / 0
Oral herpes subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 4 (0.00%) 0 / 0 0 / 0	0 / 5 (0.00%) 0 / 0 0 / 0	1 / 10 (10.00%) 0 / 1 0 / 0
Mastoiditis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 4 (0.00%) 0 / 0 0 / 0	0 / 5 (0.00%) 0 / 0 0 / 0	1 / 10 (10.00%) 0 / 1 0 / 0
Lower respiratory tract infection viral subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 4 (0.00%) 0 / 0 0 / 0	0 / 5 (0.00%) 0 / 0 0 / 0	1 / 10 (10.00%) 0 / 2 0 / 0
Lower respiratory tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 4 (0.00%) 0 / 0 0 / 0	0 / 5 (0.00%) 0 / 0 0 / 0	1 / 10 (10.00%) 0 / 1 0 / 0
Osteomyelitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 4 (0.00%) 0 / 0 0 / 0	1 / 5 (20.00%) 0 / 2 0 / 0	0 / 10 (0.00%) 0 / 0 0 / 0
Device related infection			

subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corona virus infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Central nervous system infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (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
Implant site infection			
subjects affected / exposed	1 / 4 (25.00%)	2 / 5 (40.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media acute			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overgrowth bacterial			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Food intolerance			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Idursulfase-IT 1 mg	Idursulfase-IT 30 mg	Idursulfase-IT 10 mg Comprehensive
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	5 / 5 (100.00%)	10 / 10 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain neoplasm			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Skin papilloma			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Spinal cord neoplasm			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Vascular disorders			

Blood pressure fluctuation subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	2 / 10 (20.00%) 3
Hypotension subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	3 / 5 (60.00%) 4	4 / 10 (40.00%) 6
Pallor subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	2 / 10 (20.00%) 2
Bloody discharge subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Flushing subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	2 / 5 (40.00%) 2	3 / 10 (30.00%) 5
Haematoma subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	0 / 10 (0.00%) 0
Hypertension subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	2 / 5 (40.00%) 2	3 / 10 (30.00%) 4
Surgical and medical procedures Tooth extraction subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0	0 / 10 (0.00%) 0
General disorders and administration site conditions Application site erythema subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Asthenia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 2
Catheter site bruise subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	1 / 5 (20.00%) 2	0 / 10 (0.00%) 0
Catheter site erythema			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Chills			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	3
Implant site erythema			
subjects affected / exposed	1 / 4 (25.00%)	2 / 5 (40.00%)	1 / 10 (10.00%)
occurrences (all)	1	2	1
Cyst			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Device breakage			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	3 / 10 (30.00%)
occurrences (all)	0	0	3
Device connection issue			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Device dislocation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Device malfunction			
subjects affected / exposed	1 / 4 (25.00%)	1 / 5 (20.00%)	4 / 10 (40.00%)
occurrences (all)	3	2	7
Device occlusion			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Discomfort			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	5
Energy increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Extravasation			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Face oedema			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	0 / 4 (0.00%)	2 / 5 (40.00%)	2 / 10 (20.00%)
occurrences (all)	0	2	3
Gait disturbance			
subjects affected / exposed	2 / 4 (50.00%)	3 / 5 (60.00%)	6 / 10 (60.00%)
occurrences (all)	2	10	10
Generalised oedema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Hypothermia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Implant site effusion			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	4 / 10 (40.00%)
occurrences (all)	1	0	6
Crepitations			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Irritability			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	4 / 10 (40.00%)
occurrences (all)	0	0	7
Infusion site extravasation			
subjects affected / exposed	0 / 4 (0.00%)	3 / 5 (60.00%)	3 / 10 (30.00%)
occurrences (all)	0	9	4
Malaise			
subjects affected / exposed	0 / 4 (0.00%)	2 / 5 (40.00%)	3 / 10 (30.00%)
occurrences (all)	0	3	3
Medical device complication			
subjects affected / exposed	1 / 4 (25.00%)	2 / 5 (40.00%)	1 / 10 (10.00%)
occurrences (all)	1	3	1
Oedema peripheral			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Pain			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	4 / 10 (40.00%)
occurrences (all)	0	0	8
Puncture site pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Implant site pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Implant site rash			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Implant site reaction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Implant site scar			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Implant site swelling			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	4 / 10 (40.00%)
occurrences (all)	0	1	11
Influenza like illness			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Infusion site bruising			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Local swelling			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	4 / 10 (40.00%)
occurrences (all)	0	0	6
Pyrexia			
subjects affected / exposed	3 / 4 (75.00%)	5 / 5 (100.00%)	9 / 10 (90.00%)
occurrences (all)	6	27	76
Vascular complication associated with device			
subjects affected / exposed	1 / 4 (25.00%)	5 / 5 (100.00%)	7 / 10 (70.00%)
occurrences (all)	1	20	32

Thirst subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	1 / 10 (10.00%) 1
Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	2 / 10 (20.00%) 2
Seasonal allergy subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	1 / 5 (20.00%) 1	3 / 10 (30.00%) 5
Reproductive system and breast disorders Gynaecomastia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Penile erythema subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Testicular swelling subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0	0 / 10 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Atelectasis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	3 / 10 (30.00%) 3
Adenoidal hypertrophy subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	3 / 10 (30.00%) 3
Aspiration subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 2	2 / 10 (20.00%) 2
Asthma subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 5	2 / 10 (20.00%) 4
Dyspnoea subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	4 / 10 (40.00%) 9

Epistaxis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	2 / 10 (20.00%)
occurrences (all)	0	3	5
Hypoxia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Laryngeal oedema			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Laryngospasm			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Lung disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Dysphonia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Nasal obstruction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Nasal odour			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	3
Nasal turbinate hypertrophy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Bronchomalacia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Choking			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	2 / 10 (20.00%)
occurrences (all)	0	3	3
Cough			
subjects affected / exposed	0 / 4 (0.00%)	3 / 5 (60.00%)	8 / 10 (80.00%)
occurrences (all)	0	15	42

Nasal congestion			
subjects affected / exposed	2 / 4 (50.00%)	3 / 5 (60.00%)	5 / 10 (50.00%)
occurrences (all)	5	9	18
Obstructive airways disorder			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	2 / 10 (20.00%)
occurrences (all)	0	1	3
Oropharyngeal pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Rhonchi			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	0 / 4 (0.00%)	3 / 5 (60.00%)	6 / 10 (60.00%)
occurrences (all)	0	5	14
Rhinitis allergic			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	2 / 10 (20.00%)
occurrences (all)	0	4	2
Rhinalgia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Respiratory tract congestion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Respiratory distress			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Respiration abnormal			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Rales			
subjects affected / exposed	0 / 4 (0.00%)	2 / 5 (40.00%)	0 / 10 (0.00%)
occurrences (all)	0	3	0
Pulmonary congestion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	3 / 10 (30.00%)
occurrences (all)	0	0	3

Productive cough			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Pneumonitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Pharyngeal disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	3 / 10 (30.00%)
occurrences (all)	0	0	3
Paranasal sinus hypersecretion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Wheezing			
subjects affected / exposed	0 / 4 (0.00%)	2 / 5 (40.00%)	4 / 10 (40.00%)
occurrences (all)	0	7	15
Upper respiratory tract congestion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	3 / 10 (30.00%)
occurrences (all)	0	0	8
Tracheomalacia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Tracheal disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Tachypnoea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	3
Stridor			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	2
Snoring			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Sneezing			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	2 / 10 (20.00%)
occurrences (all)	0	4	2

Sleep apnoea syndrome subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Tracheal stenosis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Psychiatric disorders			
Decreased activity subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 3
Abnormal behaviour subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 2	0 / 10 (0.00%) 0
Affect lability subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	2 / 10 (20.00%) 2
Aggression subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 8	3 / 5 (60.00%) 4	3 / 10 (30.00%) 7
Agitation subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	3 / 5 (60.00%) 5	8 / 10 (80.00%) 11
Anticipatory anxiety subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	0 / 10 (0.00%) 0
Antisocial behaviour subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 2
Anxiety subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	1 / 10 (10.00%) 4
Bruxism subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	0 / 10 (0.00%) 0
Depressed mood			

subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Depression			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Dysphemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Eating disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Impulsive behaviour			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	1 / 4 (25.00%)	3 / 5 (60.00%)	3 / 10 (30.00%)
occurrences (all)	1	6	4
Sleep disorder			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	3 / 10 (30.00%)
occurrences (all)	0	1	5
Mood swings			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Negativism			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Personality change			
subjects affected / exposed	1 / 4 (25.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	3	1	2
Regressive behaviour			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Restlessness			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	5 / 10 (50.00%)
occurrences (all)	1	0	6
Mood altered			

subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Social avoidant behaviour subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	1 / 10 (10.00%) 1
Staring subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Investigations			
Bacterial test positive subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Bacterial test subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	3 / 10 (30.00%) 4
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	2 / 10 (20.00%) 6
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 2	3 / 10 (30.00%) 10
Activated partial thromboplastin time prolonged subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Band neutrophil count increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	2 / 10 (20.00%) 2
Base excess decreased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Bilirubin conjugated increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 2
Blood albumin decreased			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Blood bicarbonate decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Blood bilirubin increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	3
Blood calcium decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	2 / 10 (20.00%)
occurrences (all)	0	1	2
Blood chloride increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	2 / 10 (20.00%)
occurrences (all)	0	1	4
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Blood lactic acid increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Blood phosphorus decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Blood phosphorus increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Blood pressure decreased			
subjects affected / exposed	2 / 4 (50.00%)	2 / 5 (40.00%)	7 / 10 (70.00%)
occurrences (all)	4	7	33
Blood pressure diastolic decreased			
subjects affected / exposed	2 / 4 (50.00%)	2 / 5 (40.00%)	8 / 10 (80.00%)
occurrences (all)	7	33	76
Blood pressure diastolic increased			
subjects affected / exposed	1 / 4 (25.00%)	2 / 5 (40.00%)	8 / 10 (80.00%)
occurrences (all)	1	11	52

CSF culture positive			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Blood pressure systolic decreased			
subjects affected / exposed	2 / 4 (50.00%)	2 / 5 (40.00%)	7 / 10 (70.00%)
occurrences (all)	7	16	96
Blood pressure systolic increased			
subjects affected / exposed	2 / 4 (50.00%)	2 / 5 (40.00%)	8 / 10 (80.00%)
occurrences (all)	10	21	130
Blood sodium increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	3 / 10 (30.00%)
occurrences (all)	0	1	3
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	3 / 10 (30.00%)
occurrences (all)	0	1	6
Blood triglycerides increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Blood urea increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Body temperature decreased			
subjects affected / exposed	1 / 4 (25.00%)	2 / 5 (40.00%)	6 / 10 (60.00%)
occurrences (all)	3	3	8
Body temperature increased			
subjects affected / exposed	1 / 4 (25.00%)	2 / 5 (40.00%)	2 / 10 (20.00%)
occurrences (all)	1	2	3
Bone density decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Breath sounds abnormal			

subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	2
C-reactive protein increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
CSF cell count increased			
subjects affected / exposed	1 / 4 (25.00%)	1 / 5 (20.00%)	7 / 10 (70.00%)
occurrences (all)	2	4	11
Blood pressure increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	6 / 10 (60.00%)
occurrences (all)	0	1	15
CSF glucose decreased			
subjects affected / exposed	0 / 4 (0.00%)	2 / 5 (40.00%)	4 / 10 (40.00%)
occurrences (all)	0	4	18
Haemoglobin decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	4 / 10 (40.00%)
occurrences (all)	0	0	8
CSF neutrophil count positive			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
CSF protein decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
CSF protein increased			
subjects affected / exposed	1 / 4 (25.00%)	3 / 5 (60.00%)	7 / 10 (70.00%)
occurrences (all)	1	10	27
CSF white blood cell count increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Carbon dioxide decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Cardiac murmur			
subjects affected / exposed	1 / 4 (25.00%)	4 / 5 (80.00%)	4 / 10 (40.00%)
occurrences (all)	2	6	4
Coronavirus test positive			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Crystal urine present			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	3 / 10 (30.00%)
occurrences (all)	0	1	7
Electroencephalogram abnormal			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	8
Haematocrit decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	4 / 10 (40.00%)
occurrences (all)	0	0	8
CSF lymphocyte count increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Heart rate decreased			
subjects affected / exposed	2 / 4 (50.00%)	2 / 5 (40.00%)	8 / 10 (80.00%)
occurrences (all)	9	20	127
Nitrite urine present			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	3
Heart rate irregular			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Heart sounds abnormal			
subjects affected / exposed	1 / 4 (25.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Iron binding capacity total decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1

Lymphocyte count decreased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Lymphocyte morphology abnormal subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Mean cell haemoglobin concentration decreased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 2
Mean cell haemoglobin decreased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Mean cell volume abnormal subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Mean cell volume decreased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	4 / 10 (40.00%) 4
Monocyte count decreased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Monocyte morphology abnormal subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	0 / 10 (0.00%) 0
Nasogastric output abnormal subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Neutrophil count decreased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	2 / 10 (20.00%) 2
Heart rate increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	4 / 10 (40.00%) 23
Nuclear magnetic resonance imaging abnormal			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Red blood cells urine			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Oxygen saturation decreased			
subjects affected / exposed	0 / 4 (0.00%)	2 / 5 (40.00%)	7 / 10 (70.00%)
occurrences (all)	0	6	26
PCO2 decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Platelet count decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Protein total decreased			
subjects affected / exposed	1 / 4 (25.00%)	2 / 5 (40.00%)	3 / 10 (30.00%)
occurrences (all)	2	2	10
Protein total increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Protein urine			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Protein urine present			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	2
Pseudomonas test positive			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Red blood cell burr cells present			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Red blood cell count decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Red blood cell count increased			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Red blood cells CSF positive			
subjects affected / exposed	1 / 4 (25.00%)	1 / 5 (20.00%)	2 / 10 (20.00%)
occurrences (all)	1	1	2
Nuclear magnetic resonance imaging brain abnormal			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Respiratory rate decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Respiratory rate increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	2
Sleep study abnormal			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Streptococcus test positive			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Thyroid function test abnormal			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Thyroxine decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Red cell distribution width increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Transaminases increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	5
Transferrin decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1

Transferrin saturation increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 2
Urine output decreased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Urobilinogen urine increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	2 / 10 (20.00%) 3
Red blood cells urine positive subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Thyroxine increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	3 / 10 (30.00%) 4
Weight decreased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
White blood cell count decreased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 3
White blood cells urine positive subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 2
Xanthochromia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Injury, poisoning and procedural complications			
Burns second degree subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Human bite subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	2 / 10 (20.00%) 4
Bite			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Avulsion fracture			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Arthropod bite			
subjects affected / exposed	1 / 4 (25.00%)	3 / 5 (60.00%)	2 / 10 (20.00%)
occurrences (all)	2	4	8
Agitation postoperative			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	5 / 10 (50.00%)
occurrences (all)	0	0	10
Accidental exposure to product			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Contusion			
subjects affected / exposed	1 / 4 (25.00%)	3 / 5 (60.00%)	8 / 10 (80.00%)
occurrences (all)	2	14	19
Excoriation			
subjects affected / exposed	0 / 4 (0.00%)	4 / 5 (80.00%)	7 / 10 (70.00%)
occurrences (all)	0	6	12
Exposure via ingestion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Eye injury			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Fall			
subjects affected / exposed	1 / 4 (25.00%)	4 / 5 (80.00%)	6 / 10 (60.00%)
occurrences (all)	1	8	19
Foreign body			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	2 / 10 (20.00%)
occurrences (all)	0	1	5
Gastrointestinal stoma complication			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Head injury			

subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	1	0	2
Burns first degree			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Periorbital haematoma			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Muscle strain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Limb crushing injury			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Ligament sprain			
subjects affected / exposed	0 / 4 (0.00%)	2 / 5 (40.00%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Laceration			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	3 / 10 (30.00%)
occurrences (all)	0	2	3
Joint dislocation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Infusion related reaction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Incision site erythema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Post procedural complication			
subjects affected / exposed	0 / 4 (0.00%)	2 / 5 (40.00%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
Procedural pain			
subjects affected / exposed	4 / 4 (100.00%)	5 / 5 (100.00%)	8 / 10 (80.00%)
occurrences (all)	5	6	30
Procedural nausea			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Procedural hypotension			
subjects affected / exposed	0 / 4 (0.00%)	2 / 5 (40.00%)	4 / 10 (40.00%)
occurrences (all)	0	2	5
Procedural headache			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Procedural complication			
subjects affected / exposed	1 / 4 (25.00%)	2 / 5 (40.00%)	2 / 10 (20.00%)
occurrences (all)	1	3	2
Post procedural swelling			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Post procedural discomfort			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Procedural site reaction			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	3 / 10 (30.00%)
occurrences (all)	0	1	3
Scar			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Scratch			
subjects affected / exposed	1 / 4 (25.00%)	3 / 5 (60.00%)	3 / 10 (30.00%)
occurrences (all)	1	5	8
Splinter			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Suture related complication			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Thermal burn			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Tracheal haemorrhage			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Tracheostomy malfunction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Traumatic haematoma			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Wound secretion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Wound dehiscence			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Traumatic lumbar puncture			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Procedural vomiting			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Congenital, familial and genetic disorders			
Congenital bowing of long bones			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Dysmorphism			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Macrogenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Skull malformation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Thalassaemia beta			

subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Cardiac disorders			
Mitral valve stenosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Aortic valve disease			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Aortic valve incompetence			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	2 / 10 (20.00%)
occurrences (all)	0	1	2
Atrioventricular block first degree			
subjects affected / exposed	0 / 4 (0.00%)	2 / 5 (40.00%)	1 / 10 (10.00%)
occurrences (all)	0	4	1
Bradycardia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	3
Cyanosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	2
Left atrial dilatation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Left atrial hypertrophy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Left ventricular hypertrophy			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Right ventricular hypertrophy			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Sinus tachycardia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0

Tachycardia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	8
Sinus bradycardia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Clonus			
subjects affected / exposed	1 / 4 (25.00%)	3 / 5 (60.00%)	2 / 10 (20.00%)
occurrences (all)	2	6	6
Carpal tunnel syndrome			
subjects affected / exposed	0 / 4 (0.00%)	3 / 5 (60.00%)	5 / 10 (50.00%)
occurrences (all)	0	4	7
Cerebral atrophy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Cerebral ventricle dilatation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Cerebrospinal fluid leakage			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Coordination abnormal			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Convulsion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	6 / 10 (60.00%)
occurrences (all)	0	1	9
Drooling			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	3
Dyskinesia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Epilepsy			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Headache			
subjects affected / exposed	0 / 4 (0.00%)	2 / 5 (40.00%)	4 / 10 (40.00%)
occurrences (all)	0	2	37
Hyperreflexia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	2	1	0
Hypersomnia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Hypertonia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Intracranial pressure increased			
subjects affected / exposed	0 / 4 (0.00%)	3 / 5 (60.00%)	1 / 10 (10.00%)
occurrences (all)	0	4	1
Lethargy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	3 / 10 (30.00%)
occurrences (all)	0	0	9
Movement disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Muscle spasticity			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Nerve compression			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	3
Parkinsonian gait			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Presyncope			
subjects affected / exposed	0 / 4 (0.00%)	2 / 5 (40.00%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
Psychomotor hyperactivity			

subjects affected / exposed	1 / 4 (25.00%)	2 / 5 (40.00%)	2 / 10 (20.00%)
occurrences (all)	1	3	3
Depressed level of consciousness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Pyramidal tract syndrome			
subjects affected / exposed	1 / 4 (25.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	2	2	0
Restless legs syndrome			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Somnolence			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Speech disorder			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Syncope			
subjects affected / exposed	1 / 4 (25.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	2	4	2
Tremor			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Radiculopathy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 4 (25.00%)	2 / 5 (40.00%)	4 / 10 (40.00%)
occurrences (all)	1	3	7
Eosinophilia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Anisocytosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1

Hypochromasia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	3
Leukocyte vacuolisation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Leukopenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Lymphadenopathy			
subjects affected / exposed	0 / 4 (0.00%)	2 / 5 (40.00%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Microcytic anaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Microcytosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	3 / 10 (30.00%)
occurrences (all)	0	0	4
Neutropenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Punctate basophilia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	4
Iron deficiency anaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Ear disorder			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Cerumen impaction			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	6 / 10 (60.00%)
occurrences (all)	0	2	16
Deafness bilateral			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Deafness neurosensory			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Deafness unilateral			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Ear discomfort			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Ear pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	2	0	2
Mastoid effusion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Middle ear effusion			
subjects affected / exposed	1 / 4 (25.00%)	1 / 5 (20.00%)	3 / 10 (30.00%)
occurrences (all)	1	1	6
Middle ear inflammation			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Motion sickness			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Otorrhoea			
subjects affected / exposed	1 / 4 (25.00%)	2 / 5 (40.00%)	5 / 10 (50.00%)
occurrences (all)	4	3	10
Tympanic membrane disorder			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	2 / 10 (20.00%)
occurrences (all)	0	1	3
Tympanic membrane hyperaemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Tympanic membrane perforation			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Mastoid disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Eye disorders			
Eye swelling			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	2 / 10 (20.00%)
occurrences (all)	0	1	2
Conjunctivitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	4 / 10 (40.00%)
occurrences (all)	0	1	6
Dry eye			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Eczema eyelids			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Eye discharge			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	3
Eye irritation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Eyelid margin crusting			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Eyelid oedema			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Glaucoma			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Lacrimation increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1

Ocular hyperaemia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Papilloedema subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Pupils unequal subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	0 / 10 (0.00%) 0
Retinal deposits subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	0 / 10 (0.00%) 0
Gastrointestinal disorders			
Chapped lips subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	1 / 10 (10.00%) 1
Aptyalism subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	0 / 10 (0.00%) 0
Constipation subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 5	7 / 10 (70.00%) 15
Dental caries subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 2	6 / 10 (60.00%) 6
Abdominal discomfort subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	3 / 10 (30.00%) 4
Abdominal distension subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0	2 / 10 (20.00%) 5
Abdominal pain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	2 / 10 (20.00%) 3
Colitis			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	2 / 4 (50.00%)	3 / 5 (60.00%)	8 / 10 (80.00%)
occurrences (all)	8	5	44
Oesophagitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Dysphagia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	3 / 10 (30.00%)
occurrences (all)	0	7	3
Eructation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Flatulence			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Gastric haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Gastritis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Gastrointestinal disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Gastrointestinal sounds abnormal			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	3 / 10 (30.00%)
occurrences (all)	0	1	4
Ileus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	3
Inguinal hernia			

subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Lip dry			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Lip swelling			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
Loose tooth			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Mucous stools			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	2 / 10 (20.00%)
occurrences (all)	0	1	2
Nausea			
subjects affected / exposed	2 / 4 (50.00%)	1 / 5 (20.00%)	3 / 10 (30.00%)
occurrences (all)	2	1	14
Dry mouth			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Periodontal disease			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Protrusion tongue			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Retching			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	3
Salivary hypersecretion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	4
Stomatitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Swollen tongue			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Tooth crowding			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Tooth loss			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	3	3
Tooth socket haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	0 / 4 (0.00%)	2 / 5 (40.00%)	1 / 10 (10.00%)
occurrences (all)	0	3	1
Umbilical hernia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	1	1	1
Vomiting			
subjects affected / exposed	2 / 4 (50.00%)	4 / 5 (80.00%)	10 / 10 (100.00%)
occurrences (all)	8	12	53
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	2
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Dandruff			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Angiokeratoma			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Dermatitis contact			

subjects affected / exposed	1 / 4 (25.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	1	1	1
Dermatitis diaper			
subjects affected / exposed	1 / 4 (25.00%)	1 / 5 (20.00%)	2 / 10 (20.00%)
occurrences (all)	2	1	3
Rash			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	7 / 10 (70.00%)
occurrences (all)	0	0	16
Pruritus allergic			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	2 / 10 (20.00%)
occurrences (all)	0	3	3
Pityriasis rosea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Petechiae			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Miliaria			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Intertrigo			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Ingrowing nail			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Hyperkeratosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Excessive granulation tissue			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Erythema			

subjects affected / exposed	1 / 4 (25.00%)	3 / 5 (60.00%)	4 / 10 (40.00%)
occurrences (all)	1	3	6
Eczema asteatotic			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Eczema			
subjects affected / exposed	1 / 4 (25.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Dry skin			
subjects affected / exposed	2 / 4 (50.00%)	2 / 5 (40.00%)	2 / 10 (20.00%)
occurrences (all)	2	4	2
Rash erythematous			
subjects affected / exposed	1 / 4 (25.00%)	2 / 5 (40.00%)	4 / 10 (40.00%)
occurrences (all)	3	4	6
Urticaria			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Swelling face			
subjects affected / exposed	0 / 4 (0.00%)	3 / 5 (60.00%)	0 / 10 (0.00%)
occurrences (all)	0	3	0
Skin lesion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Skin fissures			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Skin exfoliation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Skin disorder			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Scab			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Red man syndrome			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Rash pruritic			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
Rash papular			
subjects affected / exposed	0 / 4 (0.00%)	2 / 5 (40.00%)	0 / 10 (0.00%)
occurrences (all)	0	4	0
Rash maculo-papular			
subjects affected / exposed	0 / 4 (0.00%)	2 / 5 (40.00%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Rash macular			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Rash generalised			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Renal and urinary disorders			
Enuresis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Pollakiuria			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Proteinuria			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	4
Urinary incontinence			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	3	0	0
Urinary retention			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 5 (40.00%)	5 / 10 (50.00%)
occurrences (all)	0	2	10
Back pain			
subjects affected / exposed	1 / 4 (25.00%)	3 / 5 (60.00%)	4 / 10 (40.00%)
occurrences (all)	1	6	6
Cervical spinal stenosis			
subjects affected / exposed	0 / 4 (0.00%)	2 / 5 (40.00%)	2 / 10 (20.00%)
occurrences (all)	0	4	2
Flank pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Foot deformity			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Intervertebral disc degeneration			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Intervertebral disc protrusion			
subjects affected / exposed	0 / 4 (0.00%)	2 / 5 (40.00%)	3 / 10 (30.00%)
occurrences (all)	0	2	5
Pain in extremity			
subjects affected / exposed	0 / 4 (0.00%)	3 / 5 (60.00%)	5 / 10 (50.00%)
occurrences (all)	0	7	7
Joint range of motion decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Joint stiffness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Joint swelling			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	2	2
Knee deformity			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2

Kyphosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Limb discomfort			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Lumbar spinal stenosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Mastication disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	3
Muscle spasms			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Muscle twitching			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	4
Muscular weakness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Musculoskeletal disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Neck pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Joint contracture			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Posture abnormal			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Spinal disorder			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0

Spondylolisthesis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Synovitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Temporomandibular joint syndrome			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Tendon disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Toe walking			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	5 / 10 (50.00%)
occurrences (all)	0	1	6
Torticollis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Vertebral foraminal stenosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Scoliosis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Infections and infestations			
Ear infection			
subjects affected / exposed	1 / 4 (25.00%)	2 / 5 (40.00%)	7 / 10 (70.00%)
occurrences (all)	2	13	26
Adenovirus infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Anorectal infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Bacteraemia			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Bacterial disease carrier			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Bacterial tracheitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Bronchitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	4
Candida nappy rash			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Clostridium difficile infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Conjunctivitis bacterial			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Corona virus infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	3 / 10 (30.00%)
occurrences (all)	0	0	3
Croup infectious			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Enterobiasis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Labyrinthitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Eye infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Eyelid infection			

subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Fungal infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Fungal skin infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Furuncle			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Gastroenteritis viral			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	4 / 10 (40.00%)
occurrences (all)	0	0	6
Gastrointestinal infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Herpes simplex			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Herpes zoster			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Hordeolum			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Impetigo			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Implant site infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Influenza			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	3 / 10 (30.00%)
occurrences (all)	0	0	4
Enterovirus infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Laryngitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Paronychia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 5 (40.00%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Localised infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Lower respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	9	6
Lower respiratory tract infection viral			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Mastoiditis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Nail infection			
subjects affected / exposed	0 / 4 (0.00%)	2 / 5 (40.00%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
Nasopharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	8 / 10 (80.00%)
occurrences (all)	0	12	18
Onychomycosis			
subjects affected / exposed	0 / 4 (0.00%)	2 / 5 (40.00%)	0 / 10 (0.00%)
occurrences (all)	0	3	0
Oral herpes			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	3
Osteomyelitis			

subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Otitis externa			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	2 / 10 (20.00%)
occurrences (all)	0	1	4
Otitis media			
subjects affected / exposed	1 / 4 (25.00%)	2 / 5 (40.00%)	5 / 10 (50.00%)
occurrences (all)	1	4	32
Otitis media acute			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Otitis media chronic			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Lice infestation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Scarlet fever			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Rhinovirus infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	3 / 10 (30.00%)
occurrences (all)	0	0	4
Skin candida			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Skin infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Subcutaneous abscess			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Tinea pedis			
subjects affected / exposed	0 / 4 (0.00%)	2 / 5 (40.00%)	2 / 10 (20.00%)
occurrences (all)	0	2	3
Tooth abscess			

subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	2 / 10 (20.00%)
occurrences (all)	0	2	2
Upper respiratory tract infection			
subjects affected / exposed	3 / 4 (75.00%)	4 / 5 (80.00%)	8 / 10 (80.00%)
occurrences (all)	3	16	47
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Pharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Pharyngitis streptococcal			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	4 / 10 (40.00%)
occurrences (all)	0	0	5
Pneumonia viral			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Rhinitis			
subjects affected / exposed	1 / 4 (25.00%)	3 / 5 (60.00%)	3 / 10 (30.00%)
occurrences (all)	1	15	13
Sinusitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	5 / 10 (50.00%)
occurrences (all)	0	1	11
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	2 / 5 (40.00%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Metabolism and nutrition disorders			
Abnormal loss of weight			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Decreased appetite			
subjects affected / exposed	1 / 4 (25.00%)	1 / 5 (20.00%)	5 / 10 (50.00%)
occurrences (all)	1	1	7

Dehydration			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Hypoalbuminaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Hypokalaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Hypophagia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Pica			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 May 2010	The following changes were made as per Amendment 1: 1. Allowance for more than 1 main clinical site. 2. Revised the safety objectives of the study to emphasise that the study's primary objective and respective endpoint was the investigation of the safety and tolerability of idursulfase-IT. 3. Revised the planned assessments included in the full neurodevelopmental assessment, consistent with changes previously described in study HGT-HIT-045 Amendments 5 and 6.
20 September 2010	The following changes were made as per Amendment 2: 1. Amended the age range of eligible participants to include pediatric participants from 3 to <18 years of age with Mucopolysaccharidosis II (MPS II) who have cognitive impairment. 2. Added the Bayley Scales of Infant Development, Third Edition (BSID -III) as an alternative to the Differential Ability Scales, Second Edition (DAS -II). 3. Updated the introductory text with available information concerning the safety profiles of idursulfase-IT and Elaprase, including updated information from ongoing clinical trials. 4. Amended the schedule of study treatments and assessments for the initial treatment phase (i.e., first 6 months) of the study to be in close alignment with the schedule of study treatments and assessments for study HGT-HIT-045.
29 March 2011	The following changes were made as per Amendment 3: Mentioned that the maximum study duration was 3 years.
28 July 2011	The following changes were made as per Amendment 4: 1. Updated information about the safety of idursulfase-IT and the IDDD. 2. Updated PK sampling times.
17 July 2012	The following changes were made as per Amendment 5: 1. Updated information concerning the safety of idursulfase-IT and the IDDD. 2. Removed the 100 mg dose cohort and the addition of a 1 mg dose cohort. 3. Refined the planned statistical analysis. 4. Added guidance concerning the performance of lumbar punctures.
07 May 2013	The following changes were made as per Amendment 6: 1. Amended the secondary and exploratory study objectives and endpoints. 2. Amended the dose selection (removal of the 1 mg dose) and consequent updates to the study design and study procedures throughout the protocol. 3. Amended the study procedures sections and schedule of events for the extended treatment phase of the study to extend the maximum duration of the extension component of the protocol. 4. Added guidance concerning the introduction of a new IDDD. 5. Added a benefit/risk assessment section. 6. Added 2 new appendices to provide summaries of adverse device effects expected with the SOPH-A-PORT Mini S and PORT-A-CATH.
07 November 2013	The following changes were made as per Amendment 7: 1. Provisioned guidance concerning the reporting procedure for abuse, misuse, overdose, or medication error. 2. A new 10 mg/mL concentration of the idursulfase-IT drug product to be used added in the study. 3. Added the assessment of device leachables from residual CSF.
15 November 2013	The following changes were made as per Amendment 6.1: 1. Introduced a new 10 milligrams per millilitre (mg/mL) concentration of idursulfase-IT in the study.
16 July 2015	The following changes were made as per Amendment 8: 1. Extended the duration of study by 3 years. 2. Changed Shire Medical Monitor for the study.

03 January 2017	The following changes were made as per Amendment 9: 1. Additional guidance regarding the management of infusion reactions. 2. Reduced interval of inpatient stay after IT dosing and reduced frequency of vital sign collection after idursulfase-IT injection. 3. Eliminated blood sample collection for PK and exploratory proteomic biomarker testing, and reduced frequency of sample collection for clinical laboratory and other (anti-idursulfase antibody, GAG) tests.
17 January 2018	The following changes were made as per Amendment 10: 1. Allowance to participants reaching the age of 18 years while participating, to continue receiving the study treatment as per protocol.
14 March 2018	The following changes were made as per Amendment 11: 1. Duration of study was extended by 5 years. 2. Allowance for participants to retain a full or partial IDDD in situ after they discontinue the study, at the discretion of the investigator based upon safety assessment, with safety follow-up.
29 May 2018	The following changes were made as per Amendment 12: 1. Allowance to either the participant's parents or their guardian signing the ICF if the participant lacks mental capacity.
17 August 2021	The following changes were made as per Amendment 13: 1 Added language with regards to global health emergencies and clinical trial continuity. 2. Allowed remote source data review and verification when on-site monitoring is not possible. 3. Updated Serious Adverse Events (SAE) reporting information.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported