



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	v1 (current)
This version publication date	13 November 2024
First version publication date	13 November 2024

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

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:

A total of 15 participants with a diagnosis of Hunter Syndrome who completed the Study HGT-HIT-045 (NCT00920647) received idursulfase-IT in conjunction with elaprase therapy.

Period 1

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

Arms

Arm title	Idursulfase-IT
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Arm description:

Participants received 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	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.

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.

Number of subjects in period 1	Idursulfase-IT
Started	15
Completed	3
Not completed	12
Termination by Sponsor	2
Site Closure	1
Adverse event, non-fatal	2
Termination by Investigator	2

Reason Not Specified	5
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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	Idursulfase-IT 1 mg+10 mg
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Participants received either 1 mg idursulfase-IT initially and then switched to 10 mg idursulfase-IT after Month 7 or later or 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 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 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.

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 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.

Reporting group values	Idursulfase-IT 1 mg+10 mg	Idursulfase-IT 1 mg	Idursulfase-IT 30 mg
Number of subjects	10	4	5
Age Categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	±	5.61 ± 1.799	7.94 ± 2.706
Gender categorical Units: Subjects			
Male		4	5
Female		0	0
Race Units: Subjects			
American Indian or Alaska Native		0	0
Asian		0	1
Black or African American		0	0
Native Hawaiian or other Pacific Islander		0	0
White		2	4
Other		2	0
Ethnicity Units: Subjects			
Hispanic or Latino		0	0
Not Hispanic or Latino		4	4
Not Reported		0	1
Unknown		0	0

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

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

End points

End points 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.

Subject analysis set title	Idursulfase-IT 1 mg+10 mg
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Participants received either 1 mg idursulfase-IT initially and then switched to 10 mg idursulfase-IT after Month 7 or later or 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 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 30 mg
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Subject analysis set type	Safety analysis
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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.

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 10 mg Comprehensive
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Subject analysis set type	Safety analysis
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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.

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

End point title	Number of Participants With Clinically Significant Changes or Apparent Difference Across Treatment Groups in Laboratory Parameters and 12-lead Electrocardiogram (ECG) Findings ^[1]
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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
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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 analysis was planned for this endpoint.

End point values	Idursulfase-IT			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: participants	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 analysis was planned for this endpoint.

End point values	Idursulfase-IT			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: participants	15			

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. Number of subjects analysed indicates the number of participants with data available for analyses.

End point type	Primary
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End point timeframe:

Baseline, Month 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 analysis was planned for this endpoint.

End point values	Idursulfase-IT 1 mg+10 mg	Idursulfase-IT 1 mg	Idursulfase-IT 30 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	0 ^[4]	0 ^[5]	
Units: millimoles per litre (mmol/L)				
arithmetic mean (standard deviation)	0.523 (± 0.436)	()	()	

Notes:

[4] - No participants had data available for analyses at the specified time point.

[5] - No participants had data available for analyses at the specified time point.

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 ^[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. Number of subjects analysed indicates the number of participants with data available for analyses.

End point type	Primary
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End point timeframe:

Baseline, Month 163

Notes:

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

Justification: Only descriptive analysis was planned for this endpoint.

End point values	Idursulfase-IT 1 mg+10 mg	Idursulfase-IT 1 mg	Idursulfase-IT 30 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	0 ^[7]	0 ^[8]	
Units: 10 ⁶ /litre (L)				
arithmetic mean (standard deviation)	7.3 (± 11.85)	()	()	

Notes:

[7] - No participants had data available for analyses at the specified time point.

[8] - No participants had data available for analyses at the specified time point.

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 ^[9]
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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. Number of subjects analysed indicates the number of participants with data available for analyses.

End point type	Primary
End point timeframe:	
Baseline, Month 163	

Notes:

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

Justification: Only descriptive analysis was planned for this endpoint.

End point values	Idursulfase-IT 1 mg+10 mg	Idursulfase-IT 1 mg	Idursulfase-IT 30 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	0 ^[10]	0 ^[11]	
Units: grams per litre (g/L)				
arithmetic mean (standard deviation)	0.493 (± 0.229)	()	()	

Notes:

[10] - No participants had data available for analyses at the specified time point.

[11] - No participants had data available for analyses at the specified time point.

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 ^[12]
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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.

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:

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

Justification: Only descriptive analysis was planned for this endpoint.

End point values	Idursulfase-IT 1 mg+10 mg	Idursulfase-IT 1 mg	Idursulfase-IT 30 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	10	4	5	
Units: participants	5	3	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
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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.

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:

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

Justification: Only descriptive analysis was planned for this endpoint.

End point values	Idursulfase-IT 1 mg+10 mg	Idursulfase-IT 1 mg	Idursulfase-IT 30 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	10	4	5	
Units: participants	6	3	3	

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:

Pharmacokinetic (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 standard deviation was not estimable as there was only one participant. 9999 indicates that there were 0 participants with data available for analyses at the specified timepoint.

End point type	Secondary
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End point timeframe:

15 minutes prior to IT injection and at multiple timepoints following IT injection on Day 2 of Weeks 3, 23, Months 19, 31, and Months 43, 55, 67, and 79

End point values	Idursulfase-IT 30 mg	Idursulfase-IT 10 mg Comprehensive		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	6		
Units: hours*nanograms per millilitre (h*ng/mL)				
arithmetic mean (standard deviation)				
Week 3: Day 2 (n=0,0)	9999 (± 9999)	9999 (± 9999)		
Week 23: Day 2 (n=0,1)	9999 (± 9999)	1765 (± 999)		

Month 19: Day 2 (n=2,3)	5179 (± 2579.8)	2869 (± 563.1)		
Month 31: Day 2 (n=1,6)	4766 (± 999)	2649 (± 1334.8)		
Month 43 (n=2,4)	4395 (± 733.1)	2324 (± 203.0)		
Month 55 (n=2,3)	2445 (± 1770.8)	1636 (± 351.4)		
Month 67 (n=2,2)	3270 (± 801.6)	1649 (± 167.4)		
Month 79 (n=0,3)	9999 (± 9999)	1865 (± 775.2)		

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. 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 standard deviation was not estimable as there was only one participant. 9999 indicates that there were 0 participants with data available for analyses at the specified timepoint.

End point type	Secondary
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End point timeframe:

15 minutes prior to IT injection and at multiple timepoints following IT injection on Day 2 of Weeks 3, 23, Months 19, 31, and Months 43, 55, 67, and 79

End point values	Idursulfase-IT 30 mg	Idursulfase-IT 10 mg Comprehensive		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	7		
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Week 3: Day 2 (n=1,1)	3746 (± 999)	1214 (± 999)		
Week 23: Day 2 (n=1,1)	4855 (± 999)	1047 (± 999)		
Month 19: Day 2 (n=5,7)	3525 (± 835.5)	1633 (± 976.6)		
Month 31: Day 2 (n=4,6)	3586 (± 1056.9)	2031 (± 1081.9)		
Month 43 (n=4,4)	3141 (± 979.7)	1944 (± 295.8)		
Month 55 (n=3,6)	1466 (± 1511.8)	1356 (± 235.3)		
Month 67 (n=3,3)	2415 (± 394.8)	1247 (± 204.0)		
Month 79 (n=0,4)	9999 (± 9999)	1500 (± 347.1)		

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. 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 standard deviation was not estimable as there was only one participant. 9999 indicates that there were 0 participants with data available for analyses at the specified timepoint.

End point type	Secondary
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End point timeframe:

15 minutes prior to IT injection and at multiple timepoints following IT injection on Day 2 of Weeks 3, 23, Months 19, 31, and Months 43, 55, 67, and 79

End point values	Idursulfase-IT 30 mg	Idursulfase-IT 10 mg Comprehensive		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	7		
Units: nanograms per millilitre (ng/mL)				
arithmetic mean (standard deviation)				
Week 3: Day 2 (n=1,1)	146.75 (± 999)	43.95 (± 999)		
Week 23: Day 2 (n=1,1)	173.40 (± 999)	36.10 (± 999)		
Month 19: Day 2 (n=5,7)	156.80 (± 33.054)	76.39 (± 51.386)		
Month 31: Day 2 (n=4,6)	175.20 (± 70.083)	143.52 (± 122.774)		
Month 43 (n=4,4)	144.35 (± 44.434)	90.57 (± 28.720)		
Month 55 (n=3,6)	93.43 (± 61.406)	61.50 (± 19.330)		
Month 67 (n=3,3)	99.20 (± 19.762)	56.73 (± 12.690)		
Month 79 (n=0,4)	9999 (± 9999)	1500 (± 347.1)		

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. 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 standard deviation was not estimable as there was only one participant. 9999 indicates that there were 0 participants with data available for analyses at the specified timepoint.

End point type	Secondary
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End point timeframe:

15 minutes prior to IT injection and at multiple timepoints following IT injection on Day 2 of Weeks 3, 23, Months 19, 31, and Months 43, 55, 67, and 79

End point values	Idursulfase-IT 30 mg	Idursulfase-IT 10 mg Comprehensive		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	7		
Units: hours				
median (full range (min-max))				
Week 3: Day 2 (n=1,1)	36.07 (36.07 to 36.1)	24.03 (24.0 to 24.03)		
Week 23: Day 2 (n=1,1)	12.00 (12.0 to 12.0)	12.00 (12.0 to 12.0)		
Month 19: Day 2 (n=5,7)	24.00 (2.00 to 30.0)	12.00 (6.00 to 36.2)		
Month 31: Day 2 (n=4,6)	17.98 (6.00 to 30.1)	9.99 (1.12 to 12.0)		
Month 43 (n=4,4)	10.02 (6.03 to 12.0)	12.00 (8.00 to 12.0)		
Month 55 (n=3,6)	7.97 (2.00 to 8.00)	12.00 (6.00 to 12.0)		
Month 67 (n=3,3)	12.00 (6.00 to 30.0)	12.00 (6.00 to 12.0)		
Month 79 (n=0,4)	9999 (9999 to 9999)	10.00 (8.00 to 12.00)		

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. 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 standard deviation was not estimable as there was only one participant. 9999 indicates that there were 0 participants with data available for analyses at the specified timepoint.

End point type	Secondary
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End point timeframe:

15 minutes prior to IT injection and at multiple timepoints following IT injection on Day 2 of Weeks 3, 23, Months 19, 31, and Months 43, 55, 67, and 79

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

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. 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 standard deviation was not estimable as there was only one participant. 9999 indicates that there were 0 participants with data available for analyses at the specified timepoint.

End point type	Secondary
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End point timeframe:

15 minutes prior to IT injection and at multiple timepoints following IT injection on Day 2 of Weeks 3, 23, Months 19, 31, and Months 43, 55, 67, and 79

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

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. 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 standard deviation was not estimable as there was only one participant. 9999 indicates that there were 0 participants with data available for analyses at the specified timepoint.

End point type	Secondary
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End point timeframe:

15 minutes prior to IT injection and at multiple timepoints following IT injection on Day 2 of Weeks 3, 23, Months 19, 31, and Months 43, 55, 67, and 79

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

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Half-life (t1/2) of Idursulfase Administered as Intrathecal and in Conjunction With Elaprase

End point title	Terminal Half-life (t1/2) 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. 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 standard deviation was not estimable as there was only one participant. 9999 indicates that there were 0 participants with data available for analyses at the specified timepoint.

End point type	Secondary
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End point timeframe:

15 minutes prior to IT injection and at multiple timepoints following IT injection on Day 2 of Weeks 3, 23, Months 19, 31, and Months 43, 55, 67, and 79

End point values	Idursulfase-IT 30 mg	Idursulfase-IT 10 mg Comprehensive		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	6		
Units: hours				
median (full range (min-max))				
Week 3: Day 2 (n=0,0)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Week 23: Day 2 (n=0,1)	9999 (9999 to 9999)	22.43 (22.4 to 22.43)		
Month 19: Day 2 (n=2,3)	16.94 (14.3 to 19.6)	18.20 (16.9 to 19.4)		
Month 31: Day 2 (n=1,6)	14.16 (14.16 to 14.2)	15.57 (8.35 to 29.8)		
Month 43 (n=2,4)	10.28 (8.31 to 12.2)	10.28 (8.21 to 14.7)		
Month 55 (n=2,3)	10.75 (9.92 to 11.6)	14.21 (11.6 to 18.6)		
Month 67 (n=2,2)	15.52 (13.4 to 17.6)	13.01 (11.6 to 14.4)		
Month 79 (n=0,3)	9999 (9999 to 9999)	9.68 (6.02 to 15.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution (Vz) of Elaprase

End point title	Volume of Distribution (Vz) 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. 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 standard deviation was not estimable as there was only one participant.	
End point type	Secondary
End point timeframe:	
15 minutes prior to IV infusion and at multiple timepoints 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: 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 (± 999)			

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. 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 standard deviation was not estimable as there was only one participant.	
End point type	Secondary
End point timeframe: 15 minutes prior to IV infusion and at multiple timepoints 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 (± 999)			

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
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. 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 standard deviation was not estimable as there was only one participant.	
End point type	Secondary
End point timeframe: 15 minutes prior to IV infusion and at multiple timepoints 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: 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 (± 999)			

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. 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 standard deviation was not estimable as there was only one participant.

End point type	Secondary
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End point timeframe:

15 minutes prior to IV infusion and at multiple timepoints 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				
Units: hours				
arithmetic mean (standard deviation)				
Week 3: Day 3-7 (n=2)	6.49 (\pm 3.817)			
Week 23: Day 3-7 (n=1)	3.80 (\pm 999)			

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 [HS/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. 999 indicates that standard deviation was not estimable as there was only one participant. 9999 indicates that there were 0 participants with data available for analyses at the specified timepoint.

End point type	Secondary
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End point timeframe:

Baseline, Months 7, 55, and 139

End point values	Idursulfase-IT 1 mg+10 mg	Idursulfase-IT 1 mg	Idursulfase-IT 30 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	10	4	5	
Units: ng/mL				
arithmetic mean (standard deviation)				
Month 7 (n=2,7,5)	-1526.24 (± 638.893)	-807.50 (± 569.461)	-987.65 (± 437.885)	
Month 55 (n=0,9,3)	-1575.63 (± 906.621)	9999 (± 9999)	-974.07 (± 558.075)	
Month 139 (n=0,1,0)	-857.63 (± 999)	9999 (± 9999)	9999 (± 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)

End point description:

Change from baseline in urinary GAG 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. 9999 indicates that there were 0 participants with data available for analysis at the specified timepoint. mg GAG/mmol creatinine stands for milligrams of GAG per millimole of creatinine.

End point type | Secondary

End point timeframe:

Baseline, Months 7, 55, and 163

End point values	Idursulfase-IT 1 mg+10 mg	Idursulfase-IT 1 mg	Idursulfase-IT 30 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	6	4	5	
Units: mg GAG/mmol creatinine				
arithmetic mean (standard deviation)				
Month 7 (n=4,6,3)	-4.20 (± 4.278)	5.22 (± 6.084)	3.35 (± 1.324)	
Month 55 (n=0,7,3)	-6.83 (± 5.837)	9999 (± 9999)	6.33 (± 7.387)	
Month 163 (n=0,2,0)	-13.88 (± 5.163)	9999 (± 9999)	9999 (± 9999)	

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 1+10 mg
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Reporting group description:

Participants received either 1 mg idursulfase-IT initially and then switched to 10 mg idursulfase-IT after Month 7 or later or 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.

Serious adverse events	Idursulfase-IT 1 mg	Idursulfase-IT 30 mg	Idursulfase-IT 1+10 mg
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	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

Appendicitis			
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
Adenovirus 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
Oral herpes			
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
Mastoiditis			
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
Lower respiratory tract infection viral			
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
Lower respiratory tract 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
Osteomyelitis			
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
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 1+10 mg
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	0 / 4 (0.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	3
Hypotension			
subjects affected / exposed	0 / 4 (0.00%)	3 / 5 (60.00%)	4 / 10 (40.00%)
occurrences (all)	0	4	6

Pallor			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	2 / 10 (20.00%)
occurrences (all)	0	1	2
Bloody discharge			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Flushing			
subjects affected / exposed	0 / 4 (0.00%)	2 / 5 (40.00%)	3 / 10 (30.00%)
occurrences (all)	0	2	5
Haematoma			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	0 / 4 (0.00%)	2 / 5 (40.00%)	3 / 10 (30.00%)
occurrences (all)	0	2	4
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Application site erythema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Asthenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Catheter site bruise			
subjects affected / exposed	1 / 4 (25.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	1	2	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
Creptitations			
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	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	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 occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 3	2 / 10 (20.00%) 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	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	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	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	3
Abnormal behaviour			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Affect lability			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Aggression			
subjects affected / exposed	2 / 4 (50.00%)	3 / 5 (60.00%)	3 / 10 (30.00%)
occurrences (all)	8	4	7
Agitation			
subjects affected / exposed	1 / 4 (25.00%)	3 / 5 (60.00%)	8 / 10 (80.00%)
occurrences (all)	1	5	11
Anticipatory anxiety			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Antisocial behaviour			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Anxiety			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	4
Bruxism			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	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	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Social avoidant behaviour			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1

Starting 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 occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	2 / 10 (20.00%) 2
Blood bicarbonate decreased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 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 occurrences (all)	2 / 4 (50.00%) 10	2 / 5 (40.00%) 21	8 / 10 (80.00%) 130
Blood sodium increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Blood thyroid stimulating hormone decreased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	3 / 10 (30.00%) 3
Blood thyroid stimulating hormone increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	3 / 10 (30.00%) 6
Blood triglycerides increased subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0	0 / 10 (0.00%) 0
Blood urea increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	0 / 10 (0.00%) 0
Body temperature decreased subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 3	2 / 5 (40.00%) 3	6 / 10 (60.00%) 8
Body temperature increased subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	2 / 5 (40.00%) 2	2 / 10 (20.00%) 3
Bone density decreased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 2
Breath sounds abnormal subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	1 / 10 (10.00%) 2
C-reactive protein increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 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	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Lymphocyte morphology abnormal			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1

Mean cell haemoglobin concentration decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Mean cell haemoglobin decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Mean cell volume abnormal			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Mean cell volume decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	4 / 10 (40.00%)
occurrences (all)	0	0	4
Monocyte count decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Monocyte morphology abnormal			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Nasogastric output abnormal			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Neutrophil count decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Heart rate increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	4 / 10 (40.00%)
occurrences (all)	0	1	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	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Urine output decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	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 occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Avulsion fracture subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 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 occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	0 / 10 (0.00%) 0
Wound secretion subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	0 / 10 (0.00%) 0
Wound dehiscence subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Traumatic lumbar puncture subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0	0 / 10 (0.00%) 0
Procedural vomiting subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 2
Congenital, familial and genetic disorders			
Congenital bowing of long bones subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Dysmorphism subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	0 / 10 (0.00%) 0
Macrogenia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Skull malformation subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	0 / 10 (0.00%) 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 occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 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	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Papilloedema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Pupils unequal			

subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Retinal deposits			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Chapped lips			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Aptyalism			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	7 / 10 (70.00%)
occurrences (all)	0	5	15
Dental caries			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	6 / 10 (60.00%)
occurrences (all)	0	2	6
Abdominal discomfort			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	3 / 10 (30.00%)
occurrences (all)	0	0	4
Abdominal distension			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	1	0	5
Abdominal pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	2 / 10 (20.00%)
occurrences (all)	0	1	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 occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	0 / 10 (0.00%) 0
Toothache subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	2 / 5 (40.00%) 3	1 / 10 (10.00%) 1
Umbilical hernia subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	1 / 5 (20.00%) 1	1 / 10 (10.00%) 1
Vomiting subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 8	4 / 5 (80.00%) 12	10 / 10 (100.00%) 53
Hepatobiliary disorders Hepatomegaly subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	1 / 10 (10.00%) 2
Skin and subcutaneous tissue disorders Dermatitis allergic subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Dandruff subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Angiokeratoma subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	0 / 10 (0.00%) 0
Dermatitis contact subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	1 / 5 (20.00%) 1	1 / 10 (10.00%) 1
Dermatitis diaper subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 2	1 / 5 (20.00%) 1	2 / 10 (20.00%) 3
Rash subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	7 / 10 (70.00%) 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 occurrences (all)	0 / 4 (0.00%) 0	2 / 5 (40.00%) 2	0 / 10 (0.00%) 0
Rash macular subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Rash generalised subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	2 / 10 (20.00%) 2
Renal and urinary disorders			
Enuresis subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 2	0 / 5 (0.00%) 0	0 / 10 (0.00%) 0
Pollakiuria subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	0 / 10 (0.00%) 0
Proteinuria subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 4
Urinary incontinence subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 3	0 / 5 (0.00%) 0	0 / 10 (0.00%) 0
Urinary retention subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	2 / 5 (40.00%) 2	5 / 10 (50.00%) 10
Back pain subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	3 / 5 (60.00%) 6	4 / 10 (40.00%) 6
Cervical spinal stenosis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	2 / 5 (40.00%) 4	2 / 10 (20.00%) 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 occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Pneumonia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	4 / 10 (40.00%) 5
Pneumonia viral subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Rhinitis subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	3 / 5 (60.00%) 15	3 / 10 (30.00%) 13
Sinusitis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	5 / 10 (50.00%) 11
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	2 / 5 (40.00%) 2	0 / 10 (0.00%) 0
Metabolism and nutrition disorders			
Abnormal loss of weight subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Decreased appetite subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	1 / 5 (20.00%) 1	5 / 10 (50.00%) 7
Dehydration subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0	1 / 10 (10.00%) 1
Hypoalbuminaemia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 2
Hypokalaemia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 10 (10.00%) 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