



## Clinical trial results:

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

#### Summary

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

#### Results information

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

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | HGT-HIT-045 |
|-----------------------|-------------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Shire Human Genetic Therapies, Inc.  |
| Sponsor organisation address | 300 Shire Way, Lexington, United States, 02421   |
| Public contact               | Medical Information, Shire Human Genetic Therapies, 001 866-888-0660 ext.2 ,<br>US_ShireHGT_Medicalinformation@shire.com |
| Scientific contact           | Medical Information, Shire Human Genetic Therapies, 001 866-888-0660 ext.2 ,<br>US_ShireHGT_Medicalinformation@shire.com |

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |                 |
|--|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 17 July 2013    |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 29 October 2012 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy:

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

Evidence for comparator: -

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

Notes:

## Population of trial subjects

### Subjects enrolled per country

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

Notes:

### Subjects enrolled per age group

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

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

## Subject disposition

### Recruitment

Recruitment details:

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

### Pre-assignment

Screening details:

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

### Period 1

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

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | Control |

Arm description:

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

|   |                       |
|---|-----------------------|
| Arm type  | No intervention       |
| No investigational medicinal product assigned in this arm |                       |
| <b>Arm title</b>  | Idursulfase IT (1 mg) |

Arm description:

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

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

Dosage and administration details:

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

|                  |                        |
|------------------|------------------------|
| <b>Arm title</b> | Idursulfase IT (10 mg) |
|------------------|------------------------|

Arm description:

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

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

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

Dosage and administration details:

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

|                  |                        |
|------------------|------------------------|
| <b>Arm title</b> | Idursulfase IT (30 mg) |
|------------------|------------------------|

Arm description:

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

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

Dosage and administration details:

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

| <b>Number of subjects in period 1</b> | Control | Idursulfase IT (1 mg) | Idursulfase IT (10 mg) |
|---------------------------------------|---------|-----------------------|------------------------|
| Started                               | 4       | 4                     | 4                      |
| Completed                             | 4       | 4                     | 4                      |

| <b>Number of subjects in period 1</b> | Idursulfase IT (30 mg) |
|---------------------------------------|------------------------|
| Started                               | 4                      |
| Completed                             | 4                      |

## Baseline characteristics

### Reporting groups

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

| Reporting group values                             | Control | Idursulfase IT (1 mg) | Idursulfase IT (10 mg) |
|--|---------|-----------------------|------------------------|
| Number of subjects                                 | 4       | 4                     | 4                      |
| Age categorical                                    |         |                       |                        |
| Units: Subjects                                    |         |                       |                        |
| In utero   | 0       | 0                     | 0                      |
| Preterm newborn infants (gestational age < 37 wks) | 0       | 0                     | 0                      |
| Newborns (0-27 days)                               | 0       | 0                     | 0                      |
| Infants and toddlers (28 days-23 months)           | 0       | 0                     | 0                      |
| Children (2-11 years)                              | 4       | 4                     | 4                      |
| Adolescents (12-17 years)                          | 0       | 0                     | 0                      |
| Adults (18-64 years)                               | 0       | 0                     | 0                      |
| From 65-84 years                                   | 0       | 0                     | 0                      |
| 85 years and over                                  | 0       | 0                     | 0                      |
| Age continuous                                     |         |                       |                        |
| Units: years                                       |         |                       |                        |
| arithmetic mean                                    | 8.64    | 5.61                  | 4.34                   |
| standard deviation                                 | ± 2.462 | ± 1.799               | ± 0.829                |

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

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

## End points

### End points reporting groups

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

### Primary: Number of Serious Adverse Events (SAE)

|                                  |   |
|----------------------------------|---|
| End point title                  | Number of Serious Adverse Events (SAE) <sup>[1]</sup> |
| End point description:           |   |
| End point type                   | Primary   |
| End point timeframe:<br>6 months |   |

#### Notes:

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

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



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

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Treatment Emergent Adverse Events (AE)

|                        |   |
|------------------------|---|
| End point title        | Number of Treatment Emergent Adverse Events (AE) <sup>[2]</sup> |
| End point description: |   |
| ITT patient population |   |
| End point type         | Primary   |
| End point timeframe:   |   |
| Baseline to Week 23    |   |

Notes:

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

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

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

## Statistical analyses

No statistical analyses for this end point

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

|  |   |
|--|---|
| End point title  | Safety: Changes in Cerebrospinal Fluid (CSF) White Blood Cells (WBC) <sup>[3]</sup> |
| End point description:   |   |
| White blood cell count in CSF was monitored throughout the study as a way of assessing any potential inflammation of the meninges induced by idursulfase-IT. |   |
| End point type   | Primary   |
| End point timeframe:   |   |
| 6 months   |   |

Notes:

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

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

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

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

## Statistical analyses

No statistical analyses for this end point

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

|                        |   |
|------------------------|---|
| End point title        | Safety: Development of Anti-idursulfase Antibodies (CSF) <sup>[4]</sup> |
| End point description: | Reflects development of anti-idursulfase antibodies post baseline       |
| End point type         | Primary   |
| End point timeframe:   | 6 months  |

Notes:

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

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

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

## Statistical analyses

No statistical analyses for this end point

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

|                        |   |
|------------------------|---|
| End point title        | Safety: Development of Anti-idursulfase Antibodies (Serum) <sup>[5]</sup> |
| End point description: |   |
| End point type         | Primary   |
| End point timeframe:   | 6 months  |

Notes:

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

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

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

## Statistical analyses

No statistical analyses for this end point

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

|                 |   |
|-----------------|---|
| End point title | Clinically Significant Electrocardiogram (ECG) Findings at Any Time During the Study <sup>[6]</sup> |
|-----------------|---|

End point description:

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

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

6 months

Notes:

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

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

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

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in CSF Glycosaminoglycans (GAGs)

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

End point description:

Percent change from Baseline to Week 27.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to Week 27

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

### Statistical analyses

No statistical analyses for this end point

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

|                 |  |
|-----------------|--|
| End point title | Level of Idursulfase in the CSF Compartment Resulting From Monthly Idursulfase IT Administrations <sup>[7]</sup> |
|-----------------|--|

End point description:

Samples collected from patients treated at doses of 1 mg and 30 mg, as well as the control group, were below the lower limit of detection of the bioanalytical method (3.13 nanogram/millilitre).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 27 (end of study)

Notes:

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

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

### Statistical analyses

No statistical analyses for this end point

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

## in Conjunction With Elaprase

|                 |   |
|-----------------|---|
| End point title | Concentration of Idursulfase in the Serum After a Single Administration in Conjunction With Elaprase <sup>[8]</sup> |
|-----------------|---|

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 3

Notes:

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

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 23

Notes:

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

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

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change From Baseline in Urinary GAGs

|                 |  |
|-----------------|--|
| End point title | Percent Change From Baseline in Urinary GAGs |
|-----------------|--|

End point description:

Percent change from Baseline to Week 27.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to Week 27

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

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Time of informed consent until 30 days after the patient's end of study visit.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 12.0 |
|--------------------|------|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Control |
|-----------------------|---------|

Reporting group description:

Untreated patients

|                       |                                     |
|-----------------------|-------------------------------------|
| Reporting group title | Idursulfase Intrathecal (IT) (1 mg) |
|-----------------------|-------------------------------------|

Reporting group description: -

|                       |                        |
|-----------------------|------------------------|
| Reporting group title | Idursulfase IT (10 mg) |
|-----------------------|------------------------|

Reporting group description: -

|                       |                        |
|-----------------------|------------------------|
| Reporting group title | Idursulfase IT (30 mg) |
|-----------------------|------------------------|

Reporting group description: -

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

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



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

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

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

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

| Non-serious adverse events                            | Control         | Idursulfase Intrathecal (IT) (1 mg) | Idursulfase IT (10 mg) |
|---|-----------------|-------------------------------------|------------------------|
| Total subjects affected by non-serious adverse events |                 |                                     |                        |
| subjects affected / exposed                           | 4 / 4 (100.00%) | 4 / 4 (100.00%)                     | 4 / 4 (100.00%)        |
| Vascular disorders                                    |                 |                                     |                        |
| Blood pressure fluctuation                            |                 |                                     |                        |
| subjects affected / exposed                           | 0 / 4 (0.00%)   | 0 / 4 (0.00%)                       | 2 / 4 (50.00%)         |
| occurrences (all)                                     | 0               | 0                                   | 3                      |
| Flushing  |                 |                                     |                        |

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

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

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

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

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

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



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

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

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

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

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

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

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

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

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



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

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

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

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

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

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

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

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



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

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

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

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

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

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

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 01 February 2008 | <p>Clarify information and text related to:</p> <ul style="list-style-type: none"><li>• Safety-related stopping rules (such that if any patient experienced a study drug-related, life-threatening [Grade 4] AE or death, or if 2 or more patients experienced a Grade 3 AE considered possibly or probably related to study drug by the sponsor, then the site would be instructed to halt idursulfase-IT administration to all patients).</li></ul>  |
| 25 July 2008     | <ul style="list-style-type: none"><li>• Allow for surgical insertion of the IDDD (PORT-A-CATH device);</li><li>• Allow for the addition of 4 patients to participate in screening, baseline, and end of study procedures, but not to receive the IDDD or study drug;</li><li>• Clarify information and text related to:</li><li>• Safety-related stopping rules (such that if any patient experienced a study drug-related, life-threatening [Grade 4] AE or death, or if 2 or more patients experienced a Grade 3 AE considered possibly or probably related to study drug by the sponsor, then the site would be instructed to halt idursulfase-IT administration to all patients).</li><li>• Updating and reformatting of references.</li></ul>   |
| 29 October 2008  | <ul style="list-style-type: none"><li>• Incorporated an independent review by a DSMB</li><li>• Allow for proteomic marker testing in plasma and CSF</li><li>• Clarify information and text related to:</li><li>• The removal of the abbreviation I2S for the drug product idursulfase</li><li>• The definition of infusion-related reactions and SAE reporting</li></ul>   |
| 21 January 2009  | <ul style="list-style-type: none"><li>• Clarify information and text related to:</li><li>• Secondary endpoints (minor change in text);</li><li>• Inclusion criteria (added an alternate way to show evidence of early stage Hunter syndrome-related CNS involvement, specifically if the patient is assessed to be between 2 and 3 standard deviations below the mean overall IQ of the healthy population);</li><li>• Study procedures (clarification of study visit dates, change in text for hearing assessments, addition of X-ray to confirm placement of the device, addition of text regarding neurological screening assessments performed on Day 7);</li><li>• Clarify that the safety analysis population is to include all enrolled patients;</li><li>• Include information about an extension study.</li></ul> |
| 08 July 2009     | <ul style="list-style-type: none"><li>• Clarify information and text related to:</li><li>• Removal of redundant text from inclusion criterion 3b;</li><li>• Removal of the IDDD in patients who discontinue participation in the study;</li><li>• CSF sampling and measurement of opening pressure;</li><li>• Study procedures (components of physical examinations, timing of vision and hearing assessment, serum chemistry assessments, urinary GAG assessments, auditory brainstem response, surgical implantation of the IDDD [suture removal, removal of a nonfunctional device], performance of X-ray, timing of neurological assessments, neurodevelopmental/behavioral assessments.)</li></ul>  |

|                 |  |
|-----------------|--|
| 21 October 2009 | <ul style="list-style-type: none"> <li>• Clarify information and text related to:</li> <li>• Dose escalation guidelines (role of DSMB);</li> <li>• Inclusion criterion 1b (add documented mutation of iduronate-2 sulfatase gene as part of eligibility for the trial);</li> <li>• Inclusion criteria 3 (relating to increase in the acceptable range of IQ values – changed from “between 2 and 3 standard deviations below the mean” to “from 2 to 3.5 standard deviations below the mean”</li> <li>• Study procedures (timing of serum chemistry assessments, BRIEF neurobehavioral assessment, removal of local postoperative neurological examination at week 2);</li> <li>• Update to Medical Monitor’s contact information.</li> </ul>  |
| 23 March 2010   | <ul style="list-style-type: none"> <li>• Clarify information and text related to:</li> <li>• Inclusion criteria (increase the acceptable IQ range and description of cognitive impairment in terms of IQ score: an IQ between 77 and 47 (corresponding to a level between 1.5 and 3.5 standard deviations below the mean overall IQ of the healthy population)</li> <li>• Exclusion criteria (revision of IQ criteria consistent with change to inclusion criterion above, minor change to clarify that opening CSF pressure upon lumbar puncture may not exceed 30.0 cm H2O);</li> <li>• Study procedures (revise timing of baseline assessments to precede enrollment/randomization and to be completed in conjunction with confirmatory screening assessments, revise the naming of study visits, institute a delay between randomization and the initial study week for untreated patients to align elapsed time on study with that of treated patients, institute an interim safety follow-up telephone contact for untreated patients, increase the allowable window for the screening visit neurodevelopmental assessments);</li> <li>• Corrections or clarifications to terminologies.</li> <li>• Revise safety objectives of the study to emphasize that the study’s primary objective and respective endpoint is the investigation of the safety and tolerability of idursulfase-IT;</li> <li>• Allow for more than one main clinical site;</li> <li>• Clarify communication between the medical monitor and investigator(s) of reviewed patient safety data.</li> </ul> |
| 07 June 2010    | <ul style="list-style-type: none"> <li>• Clarify information and text related to:</li> <li>• Feed back from the clinical site regarding the labels describing timing of the study periods and study assessments. The study assessment weeks were modified to revert numbering and titles of study weeks to that described in Amendment 6;</li> <li>• Study procedures (clarify timing of randomization (Day 0), eliminate Day 2 neurological exam, correct timing of the brief neurodevelopmental assessment;</li> <li>• Revise text requiring that all deaths during the study be reported to the IEC/IRB. Expedited reports of study drug-related deaths are to be provided to the IRB; however, reporting of nonrelated deaths is not required by IEC/IRB, and the statement that details reporting unrelated deaths was stricken from the protocol.</li> </ul>   |
| 16 August 2010  | <ul style="list-style-type: none"> <li>• Clarify information and text related to:</li> <li>• Inclusion criteria modified to include:</li> <li>• Pediatric patients from 3 to 17 years of age, inclusive, with Hunter syndrome who have cognitive impairment defined as a measurable IQ of 77 or less</li> <li>• Flexibility in the protocol language such that potentially eligible patients with inadequate cognitive status for full neurodevelopmental testing may still be acceptable for participation in the study;</li> <li>• Study procedures (addition of the BSID-III to the protocol as an alternative to the DASII)</li> <li>• Text was added describing the classification of AEs with respect to study drug, study drug administration device, and associated procedures.</li> <li>• Introductory text was updated with currently available information concerning the safety profiles of idursulfase-IT and Elaprase derived from the current edition of the Idursulfase-IT Investigator’s Brochure.</li> <li>• Minor edits and/or corrections were made to more closely align in-text descriptions of study procedures with tabulations and footnotes in the Schedules of Study Procedures.</li> </ul>   |



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| 09 February 2011 | <ul style="list-style-type: none"> <li>• Clarify information and text related to:</li> <li>• The period of time for conduct of screening assessments was extended from 30 days to 60 days;</li> <li>• The timing of patient enrollment during the dose escalation process was modified such that the third and fourth patients within a dose group could both be enrolled upon confirmation of safety following administration of the first dose of study drug to the second patient (previous versions of the protocol required that dosing of the fourth patient be delayed until the third patient had received the first dose of study drug).</li> </ul>  |
| 26 April 2011    | <ul style="list-style-type: none"> <li>• Clarify information and text related to:</li> <li>• The timing of vital sign and urine GAG assessments for treated patients;</li> <li>• Updated safety information concerning idursulfase-IT and Elaprase from ongoing studies;</li> <li>• Introduce an additional dose group (Group 4) of 4 patients to receive 6 monthly doses of idursulfase-IT at a revised lowest planned dose level (1 mg) to be administered during the study. The addition of this new dose group was intended to explore the lower end of the dose-response relationship.</li> </ul>  |
| 20 July 2011     | <ul style="list-style-type: none"> <li>• Clarify information and text related to:</li> <li>• Operational aspects of the study, most notably, adjustments to the timing of PK evaluations;</li> <li>• Updated safety information concerning IDDD and an appendix intended to assist in investigation and management in the event of a mechanical IDDD failure;</li> <li>• Clarify that the 2 no-treatment patients originally intended for the 100 mg cohort would instead be randomized as part of the 1 mg cohort.</li> </ul>  |
| 10 April 2012    | <ul style="list-style-type: none"> <li>• To eliminate evaluation of idursulfase-IT at the highest initially planned dose level of 100 mg</li> <li>• Clarify information and text related to:</li> <li>• Operational aspects of the study, including clarifications to the timing of pre-treatment urine sample and PK blood sample collection, allowance of a time window for vital signs collection</li> <li>• To include up-to-date nonclinical and clinical safety data derived from the annual update of the Idursulfase-IT Investigator's Brochure (data cutoff date 19 January 2012)</li> <li>• To remove information specific to the Smith's Medical IDDD in relation to investigation and management of device failures</li> <li>• To define the Intent-to-Treat (ITT) analysis population as all randomized patients.</li> </ul> |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

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

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

Notes: