



## Clinical trial results:

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

#### Summary

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

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1               |
| This version publication date  | 13 November 2024 |
| First version publication date | 13 November 2024 |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | HGT-HIT-046 |
|-----------------------|-------------|

##### Additional study identifiers

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

Notes:

#### Sponsors

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

Notes:

#### Paediatric regulatory details

|                                                                      |                     |
|----------------------------------------------------------------------|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP)       | Yes                 |
| EMA paediatric investigation plan number(s)                          | EMA-000194-PIP20-13 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No                  |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes                 |

Notes:

## Results analysis stage

|                                                      |               |
|------------------------------------------------------|---------------|
| Analysis stage                                       | Final         |
| Date of interim/final analysis                       | 30 April 2024 |
| Is this the analysis of the primary completion data? | No            |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 30 April 2024 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy:

NA

Evidence for comparator: -

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

Notes:

## Population of trial subjects

### Subjects enrolled per country

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

Notes:

### Subjects enrolled per age group

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

|                   |   |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

## Subject disposition

### Recruitment

Recruitment details:

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

### Pre-assignment

Screening details:

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

### Period 1

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

### Arms

|           |                |
|-----------|----------------|
| Arm title | Idursulfase-IT |
|-----------|----------------|

Arm description:

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

|                                        |                       |
|----------------------------------------|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | Elaprase              |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Elaprase once every 28 days for 157.2 months.

|                                        |                                        |
|----------------------------------------|----------------------------------------|
| Investigational medicinal product name | Idursulfase-IT                         |
| Investigational medicinal product code |                                        |
| Other name                             |                                        |
| Pharmaceutical forms                   | Concentrate for solution for injection |
| Routes of administration               | Intrathecal use                        |

Dosage and administration details:

Idursulfase-IT once every 28 days for 157.2 months.

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

|                      |   |
|----------------------|---|
| Reason Not Specified | 5 |
|----------------------|---|

## Baseline characteristics

### Reporting groups

|                       |                |
|-----------------------|----------------|
| Reporting group title | Idursulfase-IT |
|-----------------------|----------------|

Reporting group description:

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

| Reporting group values | Idursulfase-IT | Total |  |
|------------------------|----------------|-------|--|
| Number of subjects     | 15             | 15    |  |
| Age Categorical        |                |       |  |
| Units: Subjects        |                |       |  |

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

### Subject analysis sets

|                            |                           |
|----------------------------|---------------------------|
| Subject analysis set title | Idursulfase-IT 1 mg+10 mg |
|----------------------------|---------------------------|

|                           |                 |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Participants received either 1 mg idursulfase-IT initially and then switched to 10 mg idursulfase-IT after Month 7 or later or received 10 mg idursulfase-IT initially intrathecally via IDDD or LP once monthly and SoC therapy of elaprase IV infusions for up to a maximum of 157.2 months.

|                            |                     |
|----------------------------|---------------------|
| Subject analysis set title | Idursulfase-IT 1 mg |
|----------------------------|---------------------|

|                           |                 |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Participants received 1 mg idursulfase-IT intrathecally via IDDD or LP once monthly and SoC therapy of

elaprase IV infusions for up to a maximum of 10.1 months.

|                            |                      |
|----------------------------|----------------------|
| Subject analysis set title | Idursulfase-IT 30 mg |
| Subject analysis set type  | Safety analysis      |

Subject analysis set description:

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

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

Subject analysis set description:

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

|                            |                                    |
|----------------------------|------------------------------------|
| Subject analysis set title | Idursulfase-IT 10 mg Comprehensive |
| Subject analysis set type  | Safety analysis                    |

Subject analysis set description:

Participants received 10 mg idursulfase-IT intrathecally via IDDD or LP once monthly and SoC therapy of elaprase IV infusions for up to a maximum of 157.2 months. This comprehensive group includes participants who received 10 mg idursulfase-IT at any point in the study.

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

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

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

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

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                     |                                    |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                               | Idursulfase-IT                     |
| Reporting group description:<br>Participants received either 10 or 30 milligrams (mg) idursulfase-IT intrathecally via intrathecal drug delivery device (IDDD) or lumbar puncture (LP) once monthly and standard-of-care (SoC) therapy of elaprase IV infusions up to a maximum of 157.2 months.                                    |                                    |
| Subject analysis set title                                                                                                                                                                                                                                                                                                          | Idursulfase-IT 1 mg+10 mg          |
| Subject analysis set type                                                                                                                                                                                                                                                                                                           | Safety analysis                    |
| Subject analysis set description:<br>Participants received either 1 mg idursulfase-IT initially and then switched to 10 mg idursulfase-IT after Month 7 or later or received 10 mg idursulfase-IT initially intrathecally via IDDD or LP once monthly and SoC therapy of elaprase IV infusions for up to a maximum of 157.2 months. |                                    |
| Subject analysis set title                                                                                                                                                                                                                                                                                                          | Idursulfase-IT 1 mg                |
| Subject analysis set type                                                                                                                                                                                                                                                                                                           | Safety analysis                    |
| Subject analysis set description:<br>Participants received 1 mg idursulfase-IT intrathecally via IDDD or LP once monthly and SoC therapy of elaprase IV infusions for up to a maximum of 10.1 months.                                                                                                                               |                                    |
| Subject analysis set title                                                                                                                                                                                                                                                                                                          | Idursulfase-IT 30 mg               |
| Subject analysis set type                                                                                                                                                                                                                                                                                                           | Safety analysis                    |
| Subject analysis set description:<br>Participants received 30 mg idursulfase-IT intrathecally via IDDD or LP once monthly and SoC therapy of elaprase IV infusions for up to a maximum of 148.2 months.                                                                                                                             |                                    |
| Subject analysis set title                                                                                                                                                                                                                                                                                                          | Elaprase IV Infusion 0.5 mg/kg     |
| Subject analysis set type                                                                                                                                                                                                                                                                                                           | Sub-group analysis                 |
| Subject analysis set description:<br>Participants received 0.5 mg/kg SoC therapy of elaprase IV infusions for up to a maximum of 157.2 months.                                                                                                                                                                                      |                                    |
| Subject analysis set title                                                                                                                                                                                                                                                                                                          | Idursulfase-IT 10 mg Comprehensive |
| Subject analysis set type                                                                                                                                                                                                                                                                                                           | Safety analysis                    |
| Subject analysis set description:<br>Participants received 10 mg idursulfase-IT intrathecally via IDDD or LP once monthly and SoC therapy of elaprase IV infusions for up to a maximum of 157.2 months. This comprehensive group includes participants who received 10 mg idursulfase-IT at any point in the study.                 |                                    |

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

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

#### Notes:

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

Justification: Only descriptive analysis was planned for this endpoint.

|                             |                 |  |  |  |
|-----------------------------|-----------------|--|--|--|
| <b>End point values</b>     | Idursulfase-IT  |  |  |  |
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 15              |  |  |  |
| Units: participants         | 0               |  |  |  |

## Statistical analyses

No statistical analyses for this end point

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

|                 |                                                                                      |
|-----------------|--------------------------------------------------------------------------------------|
| End point title | Number of Participants With Treatment-emergent Adverse Events (TEAEs) <sup>[2]</sup> |
|-----------------|--------------------------------------------------------------------------------------|

End point description:

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

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

End point timeframe:

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

Notes:

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

Justification: Only descriptive analysis was planned for this endpoint.

|                             |                 |  |  |  |
|-----------------------------|-----------------|--|--|--|
| <b>End point values</b>     | Idursulfase-IT  |  |  |  |
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 15              |  |  |  |
| Units: participants         | 15              |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: CSF Chemistries: Change from Baseline in CSF Glucose

|                 |                                                                     |
|-----------------|---------------------------------------------------------------------|
| End point title | CSF Chemistries: Change from Baseline in CSF Glucose <sup>[3]</sup> |
|-----------------|---------------------------------------------------------------------|

End point description:

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

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

End point timeframe:

Baseline, Month 163

Notes:

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

Justification: Only descriptive analysis was planned for this endpoint.

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

Notes:

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

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

## Statistical analyses

No statistical analyses for this end point

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

|                 |                                                                                                    |
|-----------------|----------------------------------------------------------------------------------------------------|
| End point title | CSF Chemistries: Change from Baseline in Cerebrospinal Fluid (CSF) Total Cell Count <sup>[6]</sup> |
|-----------------|----------------------------------------------------------------------------------------------------|

End point description:

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

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

End point timeframe:

Baseline, Month 163

Notes:

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

Justification: Only descriptive analysis was planned for this endpoint.

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

Notes:

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

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

## Statistical analyses

No statistical analyses for this end point

## Primary: CSF Chemistries: Change from Baseline in CSF Protein

|                 |                                                                     |
|-----------------|---------------------------------------------------------------------|
| End point title | CSF Chemistries: Change from Baseline in CSF Protein <sup>[9]</sup> |
|-----------------|---------------------------------------------------------------------|

End point description:

Safety Population included all eligible participants from HGT-HIT-045 who had agreed to participate in

the extension study and had either surgical implantation of an IDDD or intrathecal administration of study drug in the extension study. Number of subjects analysed indicates the number of participants with data available for analyses.

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

Notes:

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

Justification: Only descriptive analysis was planned for this endpoint.

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

Notes:

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

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

## Statistical analyses

No statistical analyses for this end point

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

|                 |                                                                                        |
|-----------------|----------------------------------------------------------------------------------------|
| End point title | Number of Participants who Reported Anti-idursulfase Antibodies in CSF <sup>[12]</sup> |
|-----------------|----------------------------------------------------------------------------------------|

End point description:

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

|                                                                            |         |
|----------------------------------------------------------------------------|---------|
| End point type                                                             | Primary |
| End point timeframe:                                                       |         |
| From start of study drug administration up to follow-up (up to 165 months) |         |

Notes:

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

Justification: Only descriptive analysis was planned for this endpoint.

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

## Statistical analyses

No statistical analyses for this end point

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

|                 |                                                      |
|-----------------|------------------------------------------------------|
| End point title | Number of Participants who Reported Anti-idursulfase |
|-----------------|------------------------------------------------------|

## End point description:

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

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

## End point timeframe:

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

## Notes:

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

Justification: Only descriptive analysis was planned for this endpoint.

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

### Statistical analyses

No statistical analyses for this end point

### Secondary: Area Under the Curve Extrapolated to Infinity (AUC<sub>0-infinity</sub>) of Idursulfase Administered as Intrathecal and in Conjunction With Elaprase

|                 |                                                                                                                                                        |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Area Under the Curve Extrapolated to Infinity (AUC <sub>0-infinity</sub> ) of Idursulfase Administered as Intrathecal and in Conjunction With Elaprase |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|

## End point description:

Pharmacokinetic (PK) population included all participants who received study drug and participated in the scheduled pharmacokinetic studies, and for whom at least 1 post-dose PK blood sample was collected. Number of subjects analysed indicates the number of participants with data available for analyses. 'n' indicates the number of participants with data available for analysis for the specified category. 999 indicates that standard deviation was not estimable as there was only one participant. 9999 indicates that there were 0 participants with data available for analyses at the specified timepoint.

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

## End point timeframe:

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

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

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

PK population included all participants who received study drug and participated in the scheduled pharmacokinetic studies, and for whom at least 1 post-dose PK blood sample was collected. Number of subjects analysed indicates the number of participants with data available for analyses. 'n' indicates the number of participants with data available for analysis for the specified category. 999 indicates that standard deviation was not estimable as there was only one participant. 9999 indicates that there were 0 participants with data available for analyses at the specified timepoint.

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

End point timeframe:

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

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

PK population included all participants who received study drug and participated in the scheduled pharmacokinetic studies, and for whom at least 1 post-dose PK blood sample was collected. Number of subjects analysed indicates the number of participants with data available for analyses. 'n' indicates the number of participants with data available for analysis for the specified category. 999 indicates that standard deviation was not estimable as there was only one participant. 9999 indicates that there were 0 participants with data available for analyses at the specified timepoint.

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

End point timeframe:

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

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

PK population included all participants who received study drug and participated in the scheduled pharmacokinetic studies, and for whom at least 1 post-dose PK blood sample was collected. Number of subjects analysed indicates the number of participants with data available for analyses. 'n' indicates the number of participants with data available for analysis for the specified category. 999 indicates that standard deviation was not estimable as there was only one participant. 9999 indicates that there were 0 participants with data available for analyses at the specified timepoint.

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

End point timeframe:

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

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

**Statistical analyses**

No statistical analyses for this end point

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

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

End point description:

PK population included all participants who received study drug and participated in the scheduled

pharmacokinetic studies, and for whom at least 1 post-dose PK blood sample was collected. Number of subjects analysed indicates the number of participants with data available for analyses. 'n' indicates the number of participants with data available for analysis for the specified category. 999 indicates that standard deviation was not estimable as there was only one participant. 9999 indicates that there were 0 participants with data available for analyses at the specified timepoint.

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

End point timeframe:

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

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

## Statistical analyses

No statistical analyses for this end point

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

|                 |                                                                                                                                                                                                                                           |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Volume of Distribution Associated With the Terminal Slope Following Extravascular Administration Divided by the Fraction of Dose Absorbed (V <sub>z</sub> /F) of Idursulfase Administered as Intrathecal and in Conjunction With Elaprase |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

PK population included all participants who received study drug and participated in the scheduled pharmacokinetic studies, and for whom at least 1 post-dose PK blood sample was collected. Number of subjects analysed indicates the number of participants with data available for analyses. 'n' indicates the number of participants with data available for analysis for the specified category. 999 indicates that standard deviation was not estimable as there was only one participant. 9999 indicates that there were 0 participants with data available for analyses at the specified timepoint.

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

End point timeframe:

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

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

PK population included all participants who received study drug and participated in the scheduled pharmacokinetic studies, and for whom at least 1 post-dose PK blood sample was collected. Number of subjects analysed indicates the number of participants with data available for analyses. 'n' indicates the number of participants with data available for analysis for the specified category. 999 indicates that standard deviation was not estimable as there was only one participant. 9999 indicates that there were 0 participants with data available for analyses at the specified timepoint.

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

End point timeframe:

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

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

## Statistical analyses

No statistical analyses for this end point

## Secondary: Terminal Half-life (t<sub>1/2</sub>) of Idursulfase Administered as Intrathecal and in Conjunction With Elaprase

|                 |                                                                                                                    |
|-----------------|--------------------------------------------------------------------------------------------------------------------|
| End point title | Terminal Half-life (t <sub>1/2</sub> ) of Idursulfase Administered as Intrathecal and in Conjunction With Elaprase |
|-----------------|--------------------------------------------------------------------------------------------------------------------|

End point description:

PK population included all participants who received study drug and participated in the scheduled pharmacokinetic studies, and for whom at least 1 post-dose PK blood sample was collected. Number of subjects analysed indicates the number of participants with data available for analyses. 'n' indicates the number of participants with data available for analysis for the specified category. 999 indicates that standard deviation was not estimable as there was only one participant. 9999 indicates that there were 0 participants with data available for analyses at the specified timepoint.

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

End point timeframe:

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

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

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

### Statistical analyses

No statistical analyses for this end point

### Secondary: Volume of Distribution (Vz) of Elaprase

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                         |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Volume of Distribution (Vz) of Elaprase |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                         |
| PK population included all participants who received study drug and participated in the scheduled pharmacokinetic studies, and for whom at least 1 post-dose PK blood sample was collected. Number of subjects analysed indicates the number of participants with data available for analyses. 'n' indicates the number of participants with data available for analysis for the specified category. 999 indicates that standard deviation was not estimable as there was only one participant. |                                         |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Secondary                               |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                         |
| 15 minutes prior to IV infusion and at multiple timepoints 24 hours during/after the IV infusion on Days 3-7 of Weeks 3 and 23                                                                                                                                                                                                                                                                                                                                                                  |                                         |

| End point values                     | Elaprase IV Infusion 0.5 mg/kg |  |  |  |
|--------------------------------------|--------------------------------|--|--|--|
| Subject group type                   | Subject analysis set           |  |  |  |
| Number of subjects analysed          | 2                              |  |  |  |
| Units: litres                        |                                |  |  |  |
| arithmetic mean (standard deviation) |                                |  |  |  |
| Week 3: Day 3-7 (n=2)                | 19.91 (± 13.874)               |  |  |  |
| Week 23: Day 3-7 (n=1)               | 34.20 (± 999)                  |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Total Body Clearance (CL) of Elaprase

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                       |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Total Body Clearance (CL) of Elaprase |
| End point description:<br>PK population included all participants who received study drug and participated in the scheduled pharmacokinetic studies, and for whom at least 1 post-dose PK blood sample was collected. Number of subjects analysed indicates the number of participants with data available for analyses. 'n' indicates the number of participants with data available for analysis for the specified category. 999 indicates that standard deviation was not estimable as there was only one participant. |                                       |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Secondary                             |
| End point timeframe:<br>15 minutes prior to IV infusion and at multiple timepoints 24 hours during/after the IV infusion on Days 3-7 of Weeks 3 and 23                                                                                                                                                                                                                                                                                                                                                                    |                                       |

| End point values                     | Elaprase IV Infusion 0.5 mg/kg |  |  |  |
|--------------------------------------|--------------------------------|--|--|--|
| Subject group type                   | Subject analysis set           |  |  |  |
| Number of subjects analysed          | 2                              |  |  |  |
| Units: L/h                           |                                |  |  |  |
| arithmetic mean (standard deviation) |                                |  |  |  |
| Week 3: Day 3-7 (n=2)                | 1.94 (± 1.677)                 |  |  |  |
| Week 23: Day 3-7 (n=1)               | 3.47 (± 999)                   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

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

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Observed Steady-state Volume of Distribution (Vss) of Elaprase |
| End point description:<br>PK population included all participants who received study drug and participated in the scheduled pharmacokinetic studies, and for whom at least 1 post-dose PK blood sample was collected. Number of subjects analysed indicates the number of participants with data available for analyses. 'n' indicates the number of participants with data available for analysis for the specified category. 999 indicates that standard deviation was not estimable as there was only one participant. |                                                                |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Secondary                                                      |
| End point timeframe:<br>15 minutes prior to IV infusion and at multiple timepoints 24 hours during/after the IV infusion on Days 3-7 of Weeks 3 and 23                                                                                                                                                                                                                                                                                                                                                                    |                                                                |

| End point values                     | Elaprase IV Infusion 0.5 mg/kg |  |  |  |
|--------------------------------------|--------------------------------|--|--|--|
| Subject group type                   | Subject analysis set           |  |  |  |
| Number of subjects analysed          | 2                              |  |  |  |
| Units: litres                        |                                |  |  |  |
| arithmetic mean (standard deviation) |                                |  |  |  |
| Week 3: Day 3-7 (n=2)                | 9.40 (± 3.464)                 |  |  |  |
| Week 23: Day 3-7 (n=1)               | 13.19 (± 999)                  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

PK population included all participants who received study drug and participated in the scheduled pharmacokinetic studies, and for whom at least 1 post-dose PK blood sample was collected. Number of subjects analysed indicates the number of participants with data available for analyses. 'n' indicates the number of participants with data available for analysis for the specified category. 999 indicates that standard deviation was not estimable as there was only one participant.

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

End point timeframe:

15 minutes prior to IV infusion and at multiple timepoints 24 hours during/after the IV infusion on Days 3-7 of Weeks 3 and 23

| End point values                     | Elaprase IV Infusion 0.5 mg/kg |  |  |  |
|--------------------------------------|--------------------------------|--|--|--|
| Subject group type                   | Subject analysis set           |  |  |  |
| Number of subjects analysed          |                                |  |  |  |
| Units: hours                         |                                |  |  |  |
| arithmetic mean (standard deviation) |                                |  |  |  |
| Week 3: Day 3-7 (n=2)                | 6.49 ( $\pm$ 3.817)            |  |  |  |
| Week 23: Day 3-7 (n=1)               | 3.80 ( $\pm$ 999)              |  |  |  |

## Statistical analyses

No statistical analyses for this end point

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

|                 |                                                              |
|-----------------|--------------------------------------------------------------|
| End point title | Change From Baseline in Cerebrospinal Fluid (CSF) Biomarkers |
|-----------------|--------------------------------------------------------------|

End point description:

Change from baseline in CSF biomarkers glycosaminoglycan (GAG [HS/DS]) was assessed. Safety Population included all eligible participants from HGT-HIT-045 who had agreed to participate in the extension study and have had either surgical implantation of an IDDD or intrathecal administration of study drug in the extension study. 999 indicates that standard deviation was not estimable as there was only one participant. 9999 indicates that there were 0 participants with data available for analyses at the specified timepoint.

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

End point timeframe:

Baseline, Months 7, 55, and 139

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

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Urinary Glycosaminoglycan (GAG)

|                 |                                                         |
|-----------------|---------------------------------------------------------|
| End point title | Change From Baseline in Urinary Glycosaminoglycan (GAG) |
|-----------------|---------------------------------------------------------|

End point description:

Change from baseline in urinary GAG was assessed. Safety Population included all eligible participants from HGT-HIT-045 who had agreed to participate in the extension study and have had either surgical implantation of an IDDD or intrathecal administration of study drug in the extension study. 9999 indicates that there were 0 participants with data available for analysis at the specified timepoint. mg GAG/mmol creatinine stands for milligrams of GAG per millimole of creatinine.

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

End point timeframe:

Baseline, Months 7, 55, and 163

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

## Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

### Reporting groups

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Idursulfase-IT 1 mg |
|-----------------------|---------------------|

Reporting group description:

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

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

Reporting group description:

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

|                       |                        |
|-----------------------|------------------------|
| Reporting group title | Idursulfase-IT 1+10 mg |
|-----------------------|------------------------|

Reporting group description:

Participants received either 1 mg idursulfase-IT initially and then switched to 10 mg idursulfase-IT after Month 7 or later or received 10 mg idursulfase-IT initially intrathecally via IDDD or LP once monthly and SoC therapy of elaprase IV infusions for up to a maximum of 157.2 months.

| Serious adverse events                               | Idursulfase-IT 1 mg | Idursulfase-IT 30 mg | Idursulfase-IT 1+10 mg |
|------------------------------------------------------|---------------------|----------------------|------------------------|
| Total subjects affected by serious adverse events    |                     |                      |                        |
| subjects affected / exposed                          | 3 / 4 (75.00%)      | 4 / 5 (80.00%)       | 9 / 10 (90.00%)        |
| number of deaths (all causes)                        | 0                   | 0                    | 0                      |
| number of deaths resulting from adverse events       | 0                   | 0                    | 0                      |
| Vascular disorders                                   |                     |                      |                        |
| Pallor                                               |                     |                      |                        |
| subjects affected / exposed                          | 0 / 4 (0.00%)       | 0 / 5 (0.00%)        | 1 / 10 (10.00%)        |
| occurrences causally related to treatment / all      | 0 / 0               | 0 / 0                | 0 / 1                  |
| deaths causally related to treatment / all           | 0 / 0               | 0 / 0                | 0 / 0                  |
| General disorders and administration site conditions |                     |                      |                        |
| Device difficult to use                              |                     |                      |                        |
| subjects affected / exposed                          | 1 / 4 (25.00%)      | 0 / 5 (0.00%)        | 0 / 10 (0.00%)         |
| occurrences causally related to treatment / all      | 0 / 1               | 0 / 0                | 0 / 0                  |
| deaths causally related to treatment / all           | 0 / 0               | 0 / 0                | 0 / 0                  |

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

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

|                                                 |               |                |                 |
|-------------------------------------------------|---------------|----------------|-----------------|
| Bronchospasm                                    |               |                |                 |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0           |
| Respiratory failure                             |               |                |                 |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0           |
| Laryngospasm                                    |               |                |                 |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0           |
| Hypoxia                                         |               |                |                 |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0           |
| Dyspnoea                                        |               |                |                 |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0           |
| Psychiatric disorders                           |               |                |                 |
| Agitation                                       |               |                |                 |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0           |
| Mental status changes                           |               |                |                 |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0           |
| Investigations                                  |               |                |                 |
| CSF white blood cell count increased            |               |                |                 |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0           |

|                                                 |                |                |                 |
|-------------------------------------------------|----------------|----------------|-----------------|
| Injury, poisoning and procedural complications  |                |                |                 |
| Feeding tube complication                       |                |                |                 |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Tracheostomy malfunction                        |                |                |                 |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Wound dehiscence                                |                |                |                 |
| subjects affected / exposed                     | 1 / 4 (25.00%) | 0 / 5 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Wound haematoma                                 |                |                |                 |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Cardiac disorders                               |                |                |                 |
| Tachycardia                                     |                |                |                 |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Nervous system disorders                        |                |                |                 |
| Convulsion                                      |                |                |                 |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 3 / 10 (30.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 6           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Atonic seizures                                 |                |                |                 |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Cerebrospinal fluid leakage                     |                |                |                 |

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

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

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

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

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

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

| <b>Non-serious adverse events</b>                                          | Idursulfase-IT 1 mg | Idursulfase-IT 30 mg | Idursulfase-IT 1+10 mg |
|----------------------------------------------------------------------------|---------------------|----------------------|------------------------|
| <b>Total subjects affected by non-serious adverse events</b>               |                     |                      |                        |
| subjects affected / exposed                                                | 4 / 4 (100.00%)     | 5 / 5 (100.00%)      | 10 / 10 (100.00%)      |
| <b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b> |                     |                      |                        |
| Brain neoplasm                                                             |                     |                      |                        |
| subjects affected / exposed                                                | 0 / 4 (0.00%)       | 0 / 5 (0.00%)        | 1 / 10 (10.00%)        |
| occurrences (all)                                                          | 0                   | 0                    | 1                      |
| Skin papilloma                                                             |                     |                      |                        |
| subjects affected / exposed                                                | 0 / 4 (0.00%)       | 0 / 5 (0.00%)        | 2 / 10 (20.00%)        |
| occurrences (all)                                                          | 0                   | 0                    | 2                      |
| Spinal cord neoplasm                                                       |                     |                      |                        |
| subjects affected / exposed                                                | 0 / 4 (0.00%)       | 0 / 5 (0.00%)        | 1 / 10 (10.00%)        |
| occurrences (all)                                                          | 0                   | 0                    | 1                      |
| <b>Vascular disorders</b>                                                  |                     |                      |                        |
| Blood pressure fluctuation                                                 |                     |                      |                        |
| subjects affected / exposed                                                | 0 / 4 (0.00%)       | 0 / 5 (0.00%)        | 2 / 10 (20.00%)        |
| occurrences (all)                                                          | 0                   | 0                    | 3                      |
| Hypotension                                                                |                     |                      |                        |
| subjects affected / exposed                                                | 0 / 4 (0.00%)       | 3 / 5 (60.00%)       | 4 / 10 (40.00%)        |
| occurrences (all)                                                          | 0                   | 4                    | 6                      |

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

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

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 2 / 4 (50.00%) | 3 / 5 (60.00%) | 6 / 10 (60.00%) |
| occurrences (all)           | 2              | 10             | 10              |
| Generalised oedema          |                |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)           | 0              | 0              | 1               |
| Hypothermia                 |                |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)           | 0              | 0              | 1               |
| Implant site effusion       |                |                |                 |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%)  | 4 / 10 (40.00%) |
| occurrences (all)           | 1              | 0              | 6               |
| Crepitations                |                |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0               |
| Irritability                |                |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 4 / 10 (40.00%) |
| occurrences (all)           | 0              | 0              | 7               |
| Infusion site extravasation |                |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 3 / 5 (60.00%) | 3 / 10 (30.00%) |
| occurrences (all)           | 0              | 9              | 4               |
| Malaise                     |                |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 2 / 5 (40.00%) | 3 / 10 (30.00%) |
| occurrences (all)           | 0              | 3              | 3               |
| Medical device complication |                |                |                 |
| subjects affected / exposed | 1 / 4 (25.00%) | 2 / 5 (40.00%) | 1 / 10 (10.00%) |
| occurrences (all)           | 1              | 3              | 1               |
| Oedema peripheral           |                |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0               |
| Pain                        |                |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 4 / 10 (40.00%) |
| occurrences (all)           | 0              | 0              | 8               |
| Puncture site pain          |                |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0               |
| Implant site pain           |                |                |                 |

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

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

|                              |                |                |                 |
|------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed  | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 1 / 10 (10.00%) |
| occurrences (all)            | 0              | 1              | 1               |
| Laryngeal oedema             |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)            | 0              | 1              | 0               |
| Laryngospasm                 |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)            | 0              | 0              | 1               |
| Lung disorder                |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)            | 0              | 0              | 2               |
| Dysphonia                    |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)            | 0              | 1              | 0               |
| Nasal obstruction            |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)            | 0              | 0              | 1               |
| Nasal odour                  |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)            | 0              | 0              | 3               |
| Nasal turbinate hypertrophy  |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)            | 0              | 0              | 1               |
| Bronchomalacia               |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)            | 0              | 0              | 1               |
| Choking                      |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 2 / 10 (20.00%) |
| occurrences (all)            | 0              | 3              | 3               |
| Cough                        |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 3 / 5 (60.00%) | 8 / 10 (80.00%) |
| occurrences (all)            | 0              | 15             | 42              |
| Nasal congestion             |                |                |                 |
| subjects affected / exposed  | 2 / 4 (50.00%) | 3 / 5 (60.00%) | 5 / 10 (50.00%) |
| occurrences (all)            | 5              | 9              | 18              |
| Obstructive airways disorder |                |                |                 |

|                              |                |                |                 |
|------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed  | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 2 / 10 (20.00%) |
| occurrences (all)            | 0              | 1              | 3               |
| Oropharyngeal pain           |                |                |                 |
| subjects affected / exposed  | 1 / 4 (25.00%) | 0 / 5 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)            | 1              | 0              | 0               |
| Rhonchi                      |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)            | 0              | 0              | 1               |
| Rhinorrhoea                  |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 3 / 5 (60.00%) | 6 / 10 (60.00%) |
| occurrences (all)            | 0              | 5              | 14              |
| Rhinitis allergic            |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 2 / 10 (20.00%) |
| occurrences (all)            | 0              | 4              | 2               |
| Rhinalgia                    |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)            | 0              | 0              | 1               |
| Respiratory tract congestion |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)            | 0              | 0              | 1               |
| Respiratory distress         |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)            | 0              | 0              | 1               |
| Respiration abnormal         |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)            | 0              | 0              | 1               |
| Rales                        |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 2 / 5 (40.00%) | 0 / 10 (0.00%)  |
| occurrences (all)            | 0              | 3              | 0               |
| Pulmonary congestion         |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 3 / 10 (30.00%) |
| occurrences (all)            | 0              | 0              | 3               |
| Productive cough             |                |                |                 |
| subjects affected / exposed  | 1 / 4 (25.00%) | 0 / 5 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)            | 1              | 0              | 0               |
| Pneumonitis                  |                |                |                 |

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

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

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

|                                                                                                        |                     |                     |                       |
|--------------------------------------------------------------------------------------------------------|---------------------|---------------------|-----------------------|
| Starting<br>subjects affected / exposed<br>occurrences (all)                                           | 1 / 4 (25.00%)<br>1 | 0 / 5 (0.00%)<br>0  | 1 / 10 (10.00%)<br>1  |
| Investigations                                                                                         |                     |                     |                       |
| Bacterial test positive<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 4 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 1 / 10 (10.00%)<br>1  |
| Bacterial test<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 4 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 3 / 10 (30.00%)<br>4  |
| Aspartate aminotransferase<br>increased<br>subjects affected / exposed<br>occurrences (all)            | 0 / 4 (0.00%)<br>0  | 1 / 5 (20.00%)<br>1 | 2 / 10 (20.00%)<br>6  |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 4 (0.00%)<br>0  | 1 / 5 (20.00%)<br>2 | 3 / 10 (30.00%)<br>10 |
| Activated partial thromboplastin time<br>prolonged<br>subjects affected / exposed<br>occurrences (all) | 0 / 4 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 1 / 10 (10.00%)<br>1  |
| Band neutrophil count increased<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 4 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 2 / 10 (20.00%)<br>2  |
| Base excess decreased<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 4 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 1 / 10 (10.00%)<br>1  |
| Bilirubin conjugated increased<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 4 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 1 / 10 (10.00%)<br>2  |
| Blood albumin decreased<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 4 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 2 / 10 (20.00%)<br>2  |
| Blood bicarbonate decreased<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 4 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 1 / 10 (10.00%)<br>1  |
| Blood bilirubin increased                                                                              |                     |                     |                       |

|                                        |                |                |                 |
|----------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed            | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 2 / 10 (20.00%) |
| occurrences (all)                      | 0              | 0              | 3               |
| Blood calcium decreased                |                |                |                 |
| subjects affected / exposed            | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 2 / 10 (20.00%) |
| occurrences (all)                      | 0              | 1              | 2               |
| Blood chloride increased               |                |                |                 |
| subjects affected / exposed            | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 2 / 10 (20.00%) |
| occurrences (all)                      | 0              | 1              | 4               |
| Blood creatine phosphokinase increased |                |                |                 |
| subjects affected / exposed            | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 1 / 10 (10.00%) |
| occurrences (all)                      | 0              | 1              | 1               |
| Blood lactic acid increased            |                |                |                 |
| subjects affected / exposed            | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                      | 0              | 0              | 1               |
| Blood phosphorus decreased             |                |                |                 |
| subjects affected / exposed            | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 1 / 10 (10.00%) |
| occurrences (all)                      | 0              | 1              | 1               |
| Blood phosphorus increased             |                |                |                 |
| subjects affected / exposed            | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                      | 0              | 0              | 1               |
| Blood pressure decreased               |                |                |                 |
| subjects affected / exposed            | 2 / 4 (50.00%) | 2 / 5 (40.00%) | 7 / 10 (70.00%) |
| occurrences (all)                      | 4              | 7              | 33              |
| Blood pressure diastolic decreased     |                |                |                 |
| subjects affected / exposed            | 2 / 4 (50.00%) | 2 / 5 (40.00%) | 8 / 10 (80.00%) |
| occurrences (all)                      | 7              | 33             | 76              |
| Blood pressure diastolic increased     |                |                |                 |
| subjects affected / exposed            | 1 / 4 (25.00%) | 2 / 5 (40.00%) | 8 / 10 (80.00%) |
| occurrences (all)                      | 1              | 11             | 52              |
| CSF culture positive                   |                |                |                 |
| subjects affected / exposed            | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                      | 0              | 1              | 0               |
| Blood pressure systolic decreased      |                |                |                 |
| subjects affected / exposed            | 2 / 4 (50.00%) | 2 / 5 (40.00%) | 7 / 10 (70.00%) |
| occurrences (all)                      | 7              | 16             | 96              |

|                                                                                                    |                      |                      |                        |
|----------------------------------------------------------------------------------------------------|----------------------|----------------------|------------------------|
| Blood pressure systolic increased<br>subjects affected / exposed<br>occurrences (all)              | 2 / 4 (50.00%)<br>10 | 2 / 5 (40.00%)<br>21 | 8 / 10 (80.00%)<br>130 |
| Blood sodium increased<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 4 (0.00%)<br>0   | 0 / 5 (0.00%)<br>0   | 1 / 10 (10.00%)<br>1   |
| Blood thyroid stimulating hormone<br>decreased<br>subjects affected / exposed<br>occurrences (all) | 0 / 4 (0.00%)<br>0   | 1 / 5 (20.00%)<br>1  | 3 / 10 (30.00%)<br>3   |
| Blood thyroid stimulating hormone<br>increased<br>subjects affected / exposed<br>occurrences (all) | 0 / 4 (0.00%)<br>0   | 1 / 5 (20.00%)<br>1  | 3 / 10 (30.00%)<br>6   |
| Blood triglycerides increased<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 4 (25.00%)<br>1  | 0 / 5 (0.00%)<br>0   | 0 / 10 (0.00%)<br>0    |
| Blood urea increased<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 4 (0.00%)<br>0   | 1 / 5 (20.00%)<br>1  | 0 / 10 (0.00%)<br>0    |
| Body temperature decreased<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 4 (25.00%)<br>3  | 2 / 5 (40.00%)<br>3  | 6 / 10 (60.00%)<br>8   |
| Body temperature increased<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 4 (25.00%)<br>1  | 2 / 5 (40.00%)<br>2  | 2 / 10 (20.00%)<br>3   |
| Bone density decreased<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 4 (0.00%)<br>0   | 0 / 5 (0.00%)<br>0   | 1 / 10 (10.00%)<br>2   |
| Breath sounds abnormal<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 4 (0.00%)<br>0   | 1 / 5 (20.00%)<br>1  | 1 / 10 (10.00%)<br>2   |
| C-reactive protein increased<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 4 (0.00%)<br>0   | 0 / 5 (0.00%)<br>0   | 1 / 10 (10.00%)<br>1   |
| CSF cell count increased                                                                           |                      |                      |                        |

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

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

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

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

|                                       |                |                |                 |
|---------------------------------------|----------------|----------------|-----------------|
| brain abnormal                        |                |                |                 |
| subjects affected / exposed           | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                     | 0              | 0              | 1               |
| Respiratory rate decreased            |                |                |                 |
| subjects affected / exposed           | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 2 / 10 (20.00%) |
| occurrences (all)                     | 0              | 0              | 2               |
| Respiratory rate increased            |                |                |                 |
| subjects affected / exposed           | 1 / 4 (25.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                     | 1              | 0              | 2               |
| Sleep study abnormal                  |                |                |                 |
| subjects affected / exposed           | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                     | 0              | 1              | 0               |
| Streptococcus test positive           |                |                |                 |
| subjects affected / exposed           | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                     | 0              | 1              | 0               |
| Thyroid function test abnormal        |                |                |                 |
| subjects affected / exposed           | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                     | 0              | 1              | 0               |
| Thyroxine decreased                   |                |                |                 |
| subjects affected / exposed           | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                     | 0              | 0              | 1               |
| Red cell distribution width increased |                |                |                 |
| subjects affected / exposed           | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 2 / 10 (20.00%) |
| occurrences (all)                     | 0              | 0              | 2               |
| Transaminases increased               |                |                |                 |
| subjects affected / exposed           | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                     | 0              | 0              | 5               |
| Transferrin decreased                 |                |                |                 |
| subjects affected / exposed           | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                     | 0              | 0              | 1               |
| Transferrin saturation increased      |                |                |                 |
| subjects affected / exposed           | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                     | 0              | 0              | 2               |
| Urine output decreased                |                |                |                 |
| subjects affected / exposed           | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                     | 0              | 0              | 1               |

|                                                                                      |                    |                    |                      |
|--------------------------------------------------------------------------------------|--------------------|--------------------|----------------------|
| Urobilinogen urine increased<br>subjects affected / exposed<br>occurrences (all)     | 0 / 4 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 | 2 / 10 (20.00%)<br>3 |
| Red blood cells urine positive<br>subjects affected / exposed<br>occurrences (all)   | 0 / 4 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 | 1 / 10 (10.00%)<br>1 |
| Thyroxine increased<br>subjects affected / exposed<br>occurrences (all)              | 0 / 4 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 | 3 / 10 (30.00%)<br>4 |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 4 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 | 1 / 10 (10.00%)<br>1 |
| White blood cell count decreased<br>subjects affected / exposed<br>occurrences (all) | 0 / 4 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 | 1 / 10 (10.00%)<br>3 |
| White blood cells urine positive<br>subjects affected / exposed<br>occurrences (all) | 0 / 4 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 | 1 / 10 (10.00%)<br>2 |
| Xanthochromia<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 4 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 | 1 / 10 (10.00%)<br>1 |
| Injury, poisoning and procedural complications                                       |                    |                    |                      |
| Burns second degree<br>subjects affected / exposed<br>occurrences (all)              | 0 / 4 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 | 1 / 10 (10.00%)<br>1 |
| Human bite<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 4 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 | 2 / 10 (20.00%)<br>4 |
| Bite<br>subjects affected / exposed<br>occurrences (all)                             | 0 / 4 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 | 1 / 10 (10.00%)<br>1 |
| Avulsion fracture<br>subjects affected / exposed<br>occurrences (all)                | 0 / 4 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 | 1 / 10 (10.00%)<br>1 |
| Arthropod bite                                                                       |                    |                    |                      |

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

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

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

|                                            |                |                |                 |
|--------------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed                | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                          | 0              | 1              | 0               |
| Wound secretion                            |                |                |                 |
| subjects affected / exposed                | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                          | 0              | 1              | 0               |
| Wound dehiscence                           |                |                |                 |
| subjects affected / exposed                | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                          | 0              | 0              | 1               |
| Traumatic lumbar puncture                  |                |                |                 |
| subjects affected / exposed                | 1 / 4 (25.00%) | 0 / 5 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                          | 1              | 0              | 0               |
| Procedural vomiting                        |                |                |                 |
| subjects affected / exposed                | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                          | 0              | 0              | 2               |
| Congenital, familial and genetic disorders |                |                |                 |
| Congenital bowing of long bones            |                |                |                 |
| subjects affected / exposed                | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                          | 0              | 0              | 1               |
| Dysmorphism                                |                |                |                 |
| subjects affected / exposed                | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                          | 0              | 1              | 0               |
| Macrogenia                                 |                |                |                 |
| subjects affected / exposed                | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                          | 0              | 0              | 1               |
| Skull malformation                         |                |                |                 |
| subjects affected / exposed                | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                          | 0              | 1              | 0               |
| Thalassaemia beta                          |                |                |                 |
| subjects affected / exposed                | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                          | 0              | 0              | 1               |
| Cardiac disorders                          |                |                |                 |
| Mitral valve stenosis                      |                |                |                 |
| subjects affected / exposed                | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                          | 0              | 0              | 1               |
| Aortic valve disease                       |                |                |                 |

|                                     |                |                |                 |
|-------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed         | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                   | 0              | 0              | 1               |
| Aortic valve incompetence           |                |                |                 |
| subjects affected / exposed         | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 2 / 10 (20.00%) |
| occurrences (all)                   | 0              | 1              | 2               |
| Atrioventricular block first degree |                |                |                 |
| subjects affected / exposed         | 0 / 4 (0.00%)  | 2 / 5 (40.00%) | 1 / 10 (10.00%) |
| occurrences (all)                   | 0              | 4              | 1               |
| Bradycardia                         |                |                |                 |
| subjects affected / exposed         | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 1 / 10 (10.00%) |
| occurrences (all)                   | 0              | 1              | 3               |
| Cyanosis                            |                |                |                 |
| subjects affected / exposed         | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 1 / 10 (10.00%) |
| occurrences (all)                   | 0              | 1              | 2               |
| Left atrial dilatation              |                |                |                 |
| subjects affected / exposed         | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                   | 0              | 0              | 1               |
| Left atrial hypertrophy             |                |                |                 |
| subjects affected / exposed         | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                   | 0              | 0              | 1               |
| Left ventricular hypertrophy        |                |                |                 |
| subjects affected / exposed         | 1 / 4 (25.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                   | 1              | 0              | 1               |
| Right ventricular hypertrophy       |                |                |                 |
| subjects affected / exposed         | 1 / 4 (25.00%) | 0 / 5 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                   | 1              | 0              | 0               |
| Sinus tachycardia                   |                |                |                 |
| subjects affected / exposed         | 1 / 4 (25.00%) | 0 / 5 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                   | 1              | 0              | 0               |
| Tachycardia                         |                |                |                 |
| subjects affected / exposed         | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 1 / 10 (10.00%) |
| occurrences (all)                   | 0              | 1              | 8               |
| Sinus bradycardia                   |                |                |                 |
| subjects affected / exposed         | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                   | 0              | 1              | 0               |
| Nervous system disorders            |                |                |                 |

|                               |                |                |                 |
|-------------------------------|----------------|----------------|-----------------|
| Clonus                        |                |                |                 |
| subjects affected / exposed   | 1 / 4 (25.00%) | 3 / 5 (60.00%) | 2 / 10 (20.00%) |
| occurrences (all)             | 2              | 6              | 6               |
| Carpal tunnel syndrome        |                |                |                 |
| subjects affected / exposed   | 0 / 4 (0.00%)  | 3 / 5 (60.00%) | 5 / 10 (50.00%) |
| occurrences (all)             | 0              | 4              | 7               |
| Cerebral atrophy              |                |                |                 |
| subjects affected / exposed   | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)             | 0              | 0              | 1               |
| Cerebral ventricle dilatation |                |                |                 |
| subjects affected / exposed   | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)             | 0              | 0              | 1               |
| Cerebrospinal fluid leakage   |                |                |                 |
| subjects affected / exposed   | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 2 / 10 (20.00%) |
| occurrences (all)             | 0              | 0              | 2               |
| Coordination abnormal         |                |                |                 |
| subjects affected / exposed   | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)             | 0              | 0              | 1               |
| Convulsion                    |                |                |                 |
| subjects affected / exposed   | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 6 / 10 (60.00%) |
| occurrences (all)             | 0              | 1              | 9               |
| Drooling                      |                |                |                 |
| subjects affected / exposed   | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)             | 0              | 0              | 3               |
| Dyskinesia                    |                |                |                 |
| subjects affected / exposed   | 1 / 4 (25.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)             | 1              | 0              | 1               |
| Epilepsy                      |                |                |                 |
| subjects affected / exposed   | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 2 / 10 (20.00%) |
| occurrences (all)             | 0              | 0              | 2               |
| Headache                      |                |                |                 |
| subjects affected / exposed   | 0 / 4 (0.00%)  | 2 / 5 (40.00%) | 4 / 10 (40.00%) |
| occurrences (all)             | 0              | 2              | 37              |
| Hyperreflexia                 |                |                |                 |
| subjects affected / exposed   | 1 / 4 (25.00%) | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)             | 2              | 1              | 0               |

|                                  |                |                |                 |
|----------------------------------|----------------|----------------|-----------------|
| Hypersomnia                      |                |                |                 |
| subjects affected / exposed      | 1 / 4 (25.00%) | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                | 1              | 1              | 0               |
| Hypertonia                       |                |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                | 0              | 0              | 1               |
| Intracranial pressure increased  |                |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%)  | 3 / 5 (60.00%) | 1 / 10 (10.00%) |
| occurrences (all)                | 0              | 4              | 1               |
| Lethargy                         |                |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 3 / 10 (30.00%) |
| occurrences (all)                | 0              | 0              | 9               |
| Movement disorder                |                |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                | 0              | 0              | 1               |
| Muscle spasticity                |                |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                | 0              | 0              | 1               |
| Nerve compression                |                |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                | 0              | 0              | 3               |
| Parkinsonian gait                |                |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                | 0              | 0              | 2               |
| Presyncope                       |                |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%)  | 2 / 5 (40.00%) | 1 / 10 (10.00%) |
| occurrences (all)                | 0              | 2              | 1               |
| Psychomotor hyperactivity        |                |                |                 |
| subjects affected / exposed      | 1 / 4 (25.00%) | 2 / 5 (40.00%) | 2 / 10 (20.00%) |
| occurrences (all)                | 1              | 3              | 3               |
| Depressed level of consciousness |                |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                | 0              | 0              | 1               |
| Pyramidal tract syndrome         |                |                |                 |
| subjects affected / exposed      | 1 / 4 (25.00%) | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                | 2              | 2              | 0               |

|                                                                             |                     |                     |                      |
|-----------------------------------------------------------------------------|---------------------|---------------------|----------------------|
| Restless legs syndrome<br>subjects affected / exposed<br>occurrences (all)  | 0 / 4 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 1 / 10 (10.00%)<br>1 |
| Somnolence<br>subjects affected / exposed<br>occurrences (all)              | 0 / 4 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 1 / 10 (10.00%)<br>2 |
| Speech disorder<br>subjects affected / exposed<br>occurrences (all)         | 0 / 4 (0.00%)<br>0  | 1 / 5 (20.00%)<br>1 | 0 / 10 (0.00%)<br>0  |
| Syncope<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 4 (25.00%)<br>2 | 1 / 5 (20.00%)<br>4 | 1 / 10 (10.00%)<br>2 |
| Tremor<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 4 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 1 / 10 (10.00%)<br>1 |
| Radiculopathy<br>subjects affected / exposed<br>occurrences (all)           | 0 / 4 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 1 / 10 (10.00%)<br>2 |
| Blood and lymphatic system disorders                                        |                     |                     |                      |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 4 (25.00%)<br>1 | 2 / 5 (40.00%)<br>3 | 4 / 10 (40.00%)<br>7 |
| Eosinophilia<br>subjects affected / exposed<br>occurrences (all)            | 1 / 4 (25.00%)<br>1 | 0 / 5 (0.00%)<br>0  | 0 / 10 (0.00%)<br>0  |
| Anisocytosis<br>subjects affected / exposed<br>occurrences (all)            | 0 / 4 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 1 / 10 (10.00%)<br>1 |
| Hypochromasia<br>subjects affected / exposed<br>occurrences (all)           | 0 / 4 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 2 / 10 (20.00%)<br>3 |
| Leukocyte vacuolisation<br>subjects affected / exposed<br>occurrences (all) | 0 / 4 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 1 / 10 (10.00%)<br>1 |
| Leukopenia                                                                  |                     |                     |                      |

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

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

|                             |               |                |                 |
|-----------------------------|---------------|----------------|-----------------|
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 2 / 10 (20.00%) |
| occurrences (all)           | 0             | 1              | 2               |
| Conjunctivitis              |               |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 4 / 10 (40.00%) |
| occurrences (all)           | 0             | 1              | 6               |
| Dry eye                     |               |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)           | 0             | 0              | 1               |
| Eczema eyelids              |               |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)           | 0             | 1              | 0               |
| Eye discharge               |               |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)           | 0             | 0              | 3               |
| Eye irritation              |               |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)           | 0             | 0              | 2               |
| Eyelid margin crusting      |               |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)           | 0             | 0              | 1               |
| Eyelid oedema               |               |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 1 / 10 (10.00%) |
| occurrences (all)           | 0             | 1              | 1               |
| Glaucoma                    |               |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)           | 0             | 2              | 0               |
| Lacrimation increased       |               |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)           | 0             | 0              | 1               |
| Ocular hyperaemia           |               |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)           | 0             | 0              | 1               |
| Papilloedema                |               |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)           | 0             | 0              | 1               |
| Pupils unequal              |               |                |                 |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0               |
| Retinal deposits            |                |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0               |
| Gastrointestinal disorders  |                |                |                 |
| Chapped lips                |                |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 1 / 10 (10.00%) |
| occurrences (all)           | 0              | 1              | 1               |
| Aptyalism                   |                |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0               |
| Constipation                |                |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 7 / 10 (70.00%) |
| occurrences (all)           | 0              | 5              | 15              |
| Dental caries               |                |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 6 / 10 (60.00%) |
| occurrences (all)           | 0              | 2              | 6               |
| Abdominal discomfort        |                |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 3 / 10 (30.00%) |
| occurrences (all)           | 0              | 0              | 4               |
| Abdominal distension        |                |                |                 |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%)  | 2 / 10 (20.00%) |
| occurrences (all)           | 1              | 0              | 5               |
| Abdominal pain              |                |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 2 / 10 (20.00%) |
| occurrences (all)           | 0              | 1              | 3               |
| Colitis                     |                |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)           | 0              | 0              | 1               |
| Diarrhoea                   |                |                |                 |
| subjects affected / exposed | 2 / 4 (50.00%) | 3 / 5 (60.00%) | 8 / 10 (80.00%) |
| occurrences (all)           | 8              | 5              | 44              |
| Oesophagitis                |                |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)           | 0              | 0              | 1               |

|                                  |               |                |                 |
|----------------------------------|---------------|----------------|-----------------|
| Dysphagia                        |               |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 3 / 10 (30.00%) |
| occurrences (all)                | 0             | 7              | 3               |
| Eructation                       |               |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                | 0             | 0              | 1               |
| Flatulence                       |               |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                | 0             | 0              | 1               |
| Gastric haemorrhage              |               |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                | 0             | 1              | 0               |
| Gastritis                        |               |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                | 0             | 0              | 1               |
| Gastrointestinal disorder        |               |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 2 / 10 (20.00%) |
| occurrences (all)                | 0             | 0              | 2               |
| Gastrointestinal sounds abnormal |               |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                | 0             | 0              | 2               |
| Gastrooesophageal reflux disease |               |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 3 / 10 (30.00%) |
| occurrences (all)                | 0             | 1              | 4               |
| Ileus                            |               |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                | 0             | 0              | 3               |
| Inguinal hernia                  |               |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                | 0             | 2              | 0               |
| Lip dry                          |               |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 1 / 10 (10.00%) |
| occurrences (all)                | 0             | 1              | 1               |
| Lip swelling                     |               |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 1 / 10 (10.00%) |
| occurrences (all)                | 0             | 2              | 1               |

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

|                                                                                                                   |                     |                      |                         |
|-------------------------------------------------------------------------------------------------------------------|---------------------|----------------------|-------------------------|
| Tooth socket haemorrhage<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 4 (0.00%)<br>0  | 1 / 5 (20.00%)<br>1  | 0 / 10 (0.00%)<br>0     |
| Toothache<br>subjects affected / exposed<br>occurrences (all)                                                     | 0 / 4 (0.00%)<br>0  | 2 / 5 (40.00%)<br>3  | 1 / 10 (10.00%)<br>1    |
| Umbilical hernia<br>subjects affected / exposed<br>occurrences (all)                                              | 1 / 4 (25.00%)<br>1 | 1 / 5 (20.00%)<br>1  | 1 / 10 (10.00%)<br>1    |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                                                      | 2 / 4 (50.00%)<br>8 | 4 / 5 (80.00%)<br>12 | 10 / 10 (100.00%)<br>53 |
| Hepatobiliary disorders<br>Hepatomegaly<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 4 (0.00%)<br>0  | 1 / 5 (20.00%)<br>1  | 1 / 10 (10.00%)<br>2    |
| Skin and subcutaneous tissue disorders<br>Dermatitis allergic<br>subjects affected / exposed<br>occurrences (all) | 0 / 4 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0   | 1 / 10 (10.00%)<br>1    |
| Dandruff<br>subjects affected / exposed<br>occurrences (all)                                                      | 0 / 4 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0   | 1 / 10 (10.00%)<br>1    |
| Angiokeratoma<br>subjects affected / exposed<br>occurrences (all)                                                 | 0 / 4 (0.00%)<br>0  | 1 / 5 (20.00%)<br>1  | 0 / 10 (0.00%)<br>0     |
| Dermatitis contact<br>subjects affected / exposed<br>occurrences (all)                                            | 1 / 4 (25.00%)<br>1 | 1 / 5 (20.00%)<br>1  | 1 / 10 (10.00%)<br>1    |
| Dermatitis diaper<br>subjects affected / exposed<br>occurrences (all)                                             | 1 / 4 (25.00%)<br>2 | 1 / 5 (20.00%)<br>1  | 2 / 10 (20.00%)<br>3    |
| Rash<br>subjects affected / exposed<br>occurrences (all)                                                          | 0 / 4 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0   | 7 / 10 (70.00%)<br>16   |
| Pruritus allergic                                                                                                 |                     |                      |                         |

|                              |                |                |                 |
|------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed  | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)            | 0              | 0              | 1               |
| Pruritus                     |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 2 / 10 (20.00%) |
| occurrences (all)            | 0              | 3              | 3               |
| Pityriasis rosea             |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)            | 0              | 0              | 1               |
| Petechiae                    |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)            | 0              | 2              | 0               |
| Miliaria                     |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)            | 0              | 1              | 0               |
| Intertrigo                   |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)            | 0              | 1              | 0               |
| Ingrowing nail               |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)            | 0              | 1              | 0               |
| Hyperkeratosis               |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)            | 0              | 0              | 1               |
| Excessive granulation tissue |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)            | 0              | 1              | 0               |
| Erythema                     |                |                |                 |
| subjects affected / exposed  | 1 / 4 (25.00%) | 3 / 5 (60.00%) | 4 / 10 (40.00%) |
| occurrences (all)            | 1              | 3              | 6               |
| Eczema asteatotic            |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)            | 0              | 0              | 1               |
| Eczema                       |                |                |                 |
| subjects affected / exposed  | 1 / 4 (25.00%) | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)            | 1              | 1              | 0               |
| Dry skin                     |                |                |                 |

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

|                                                                              |                     |                     |                       |
|------------------------------------------------------------------------------|---------------------|---------------------|-----------------------|
| subjects affected / exposed<br>occurrences (all)                             | 0 / 4 (0.00%)<br>0  | 2 / 5 (40.00%)<br>2 | 0 / 10 (0.00%)<br>0   |
| Rash macular<br>subjects affected / exposed<br>occurrences (all)             | 0 / 4 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 1 / 10 (10.00%)<br>1  |
| Rash generalised<br>subjects affected / exposed<br>occurrences (all)         | 0 / 4 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 2 / 10 (20.00%)<br>2  |
| Renal and urinary disorders                                                  |                     |                     |                       |
| Enuresis<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 4 (25.00%)<br>2 | 0 / 5 (0.00%)<br>0  | 0 / 10 (0.00%)<br>0   |
| Pollakiuria<br>subjects affected / exposed<br>occurrences (all)              | 0 / 4 (0.00%)<br>0  | 1 / 5 (20.00%)<br>1 | 0 / 10 (0.00%)<br>0   |
| Proteinuria<br>subjects affected / exposed<br>occurrences (all)              | 0 / 4 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 1 / 10 (10.00%)<br>4  |
| Urinary incontinence<br>subjects affected / exposed<br>occurrences (all)     | 1 / 4 (25.00%)<br>3 | 0 / 5 (0.00%)<br>0  | 0 / 10 (0.00%)<br>0   |
| Urinary retention<br>subjects affected / exposed<br>occurrences (all)        | 0 / 4 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 1 / 10 (10.00%)<br>1  |
| Musculoskeletal and connective tissue disorders                              |                     |                     |                       |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)               | 0 / 4 (0.00%)<br>0  | 2 / 5 (40.00%)<br>2 | 5 / 10 (50.00%)<br>10 |
| Back pain<br>subjects affected / exposed<br>occurrences (all)                | 1 / 4 (25.00%)<br>1 | 3 / 5 (60.00%)<br>6 | 4 / 10 (40.00%)<br>6  |
| Cervical spinal stenosis<br>subjects affected / exposed<br>occurrences (all) | 0 / 4 (0.00%)<br>0  | 2 / 5 (40.00%)<br>4 | 2 / 10 (20.00%)<br>2  |
| Flank pain                                                                   |                     |                     |                       |

|                                  |               |                |                 |
|----------------------------------|---------------|----------------|-----------------|
| subjects affected / exposed      | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                | 0             | 0              | 1               |
| Foot deformity                   |               |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                | 0             | 0              | 1               |
| Intervertebral disc degeneration |               |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                | 0             | 0              | 1               |
| Intervertebral disc protrusion   |               |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%) | 2 / 5 (40.00%) | 3 / 10 (30.00%) |
| occurrences (all)                | 0             | 2              | 5               |
| Pain in extremity                |               |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%) | 3 / 5 (60.00%) | 5 / 10 (50.00%) |
| occurrences (all)                | 0             | 7              | 7               |
| Joint range of motion decreased  |               |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 1 / 10 (10.00%) |
| occurrences (all)                | 0             | 1              | 1               |
| Joint stiffness                  |               |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                | 0             | 0              | 1               |
| Joint swelling                   |               |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 1 / 10 (10.00%) |
| occurrences (all)                | 0             | 2              | 2               |
| Knee deformity                   |               |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 2 / 10 (20.00%) |
| occurrences (all)                | 0             | 0              | 2               |
| Kyphosis                         |               |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                | 0             | 1              | 0               |
| Limb discomfort                  |               |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                | 0             | 0              | 1               |
| Lumbar spinal stenosis           |               |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                | 0             | 0              | 1               |
| Mastication disorder             |               |                |                 |

|                                  |               |                |                 |
|----------------------------------|---------------|----------------|-----------------|
| subjects affected / exposed      | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                | 0             | 0              | 3               |
| Muscle spasms                    |               |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 2 / 10 (20.00%) |
| occurrences (all)                | 0             | 0              | 2               |
| Muscle twitching                 |               |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                | 0             | 0              | 4               |
| Muscular weakness                |               |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                | 0             | 0              | 1               |
| Musculoskeletal disorder         |               |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                | 0             | 0              | 1               |
| Neck pain                        |               |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                | 0             | 0              | 1               |
| Joint contracture                |               |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                | 0             | 0              | 1               |
| Posture abnormal                 |               |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 1 / 10 (10.00%) |
| occurrences (all)                | 0             | 1              | 1               |
| Spinal disorder                  |               |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                | 0             | 1              | 0               |
| Spondylolisthesis                |               |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                | 0             | 0              | 1               |
| Synovitis                        |               |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                | 0             | 0              | 2               |
| Temporomandibular joint syndrome |               |                |                 |
| subjects affected / exposed      | 0 / 4 (0.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                | 0             | 0              | 1               |
| Tendon disorder                  |               |                |                 |

|                              |                |                |                 |
|------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed  | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)            | 0              | 0              | 1               |
| Toe walking                  |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 5 / 10 (50.00%) |
| occurrences (all)            | 0              | 1              | 6               |
| Torticollis                  |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)            | 0              | 0              | 1               |
| Vertebral foraminal stenosis |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)            | 0              | 1              | 0               |
| Scoliosis                    |                |                |                 |
| subjects affected / exposed  | 1 / 4 (25.00%) | 0 / 5 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)            | 2              | 0              | 0               |
| Infections and infestations  |                |                |                 |
| Ear infection                |                |                |                 |
| subjects affected / exposed  | 1 / 4 (25.00%) | 2 / 5 (40.00%) | 7 / 10 (70.00%) |
| occurrences (all)            | 2              | 13             | 26              |
| Adenovirus infection         |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)            | 0              | 1              | 0               |
| Anorectal infection          |                |                |                 |
| subjects affected / exposed  | 1 / 4 (25.00%) | 0 / 5 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)            | 1              | 0              | 0               |
| Bacteraemia                  |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)            | 0              | 0              | 1               |
| Bacterial disease carrier    |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)            | 0              | 0              | 1               |
| Bacterial tracheitis         |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)            | 0              | 0              | 1               |
| Bronchitis                   |                |                |                 |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 2 / 10 (20.00%) |
| occurrences (all)            | 0              | 0              | 4               |

|                                 |                |                |                 |
|---------------------------------|----------------|----------------|-----------------|
| Candida nappy rash              |                |                |                 |
| subjects affected / exposed     | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)               | 0              | 0              | 1               |
| Clostridium difficile infection |                |                |                 |
| subjects affected / exposed     | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)               | 0              | 0              | 2               |
| Conjunctivitis bacterial        |                |                |                 |
| subjects affected / exposed     | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)               | 0              | 0              | 1               |
| Corona virus infection          |                |                |                 |
| subjects affected / exposed     | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 3 / 10 (30.00%) |
| occurrences (all)               | 0              | 0              | 3               |
| Croup infectious                |                |                |                 |
| subjects affected / exposed     | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 1 / 10 (10.00%) |
| occurrences (all)               | 0              | 1              | 1               |
| Enterobiasis                    |                |                |                 |
| subjects affected / exposed     | 1 / 4 (25.00%) | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)               | 1              | 0              | 1               |
| Labyrinthitis                   |                |                |                 |
| subjects affected / exposed     | 1 / 4 (25.00%) | 0 / 5 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)               | 2              | 0              | 0               |
| Eye infection                   |                |                |                 |
| subjects affected / exposed     | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)               | 0              | 1              | 0               |
| Eyelid infection                |                |                |                 |
| subjects affected / exposed     | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)               | 0              | 1              | 0               |
| Fungal infection                |                |                |                 |
| subjects affected / exposed     | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)               | 0              | 0              | 2               |
| Fungal skin infection           |                |                |                 |
| subjects affected / exposed     | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 1 / 10 (10.00%) |
| occurrences (all)               | 0              | 1              | 1               |
| Furuncle                        |                |                |                 |
| subjects affected / exposed     | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)               | 0              | 0              | 1               |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| Gastroenteritis             |                |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)           | 0              | 0              | 1               |
| Gastroenteritis viral       |                |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 4 / 10 (40.00%) |
| occurrences (all)           | 0              | 0              | 6               |
| Gastrointestinal infection  |                |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)           | 0              | 0              | 2               |
| Herpes simplex              |                |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)           | 0              | 0              | 2               |
| Herpes zoster               |                |                |                 |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)           | 2              | 0              | 0               |
| Hordeolum                   |                |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 1 / 10 (10.00%) |
| occurrences (all)           | 0              | 1              | 1               |
| Impetigo                    |                |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 1 / 10 (10.00%) |
| occurrences (all)           | 0              | 1              | 1               |
| Implant site infection      |                |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0               |
| Influenza                   |                |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 3 / 10 (30.00%) |
| occurrences (all)           | 0              | 0              | 4               |
| Enterovirus infection       |                |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)           | 0              | 0              | 1               |
| Laryngitis                  |                |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0               |
| Paronychia                  |                |                |                 |
| subjects affected / exposed | 0 / 4 (0.00%)  | 2 / 5 (40.00%) | 0 / 10 (0.00%)  |
| occurrences (all)           | 0              | 2              | 0               |

|                                         |                |                |                 |
|-----------------------------------------|----------------|----------------|-----------------|
| Localised infection                     |                |                |                 |
| subjects affected / exposed             | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 1 / 10 (10.00%) |
| occurrences (all)                       | 0              | 1              | 1               |
| Lower respiratory tract infection       |                |                |                 |
| subjects affected / exposed             | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 1 / 10 (10.00%) |
| occurrences (all)                       | 0              | 9              | 6               |
| Lower respiratory tract infection viral |                |                |                 |
| subjects affected / exposed             | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                       | 0              | 0              | 1               |
| Mastoiditis                             |                |                |                 |
| subjects affected / exposed             | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                       | 0              | 0              | 1               |
| Nail infection                          |                |                |                 |
| subjects affected / exposed             | 0 / 4 (0.00%)  | 2 / 5 (40.00%) | 1 / 10 (10.00%) |
| occurrences (all)                       | 0              | 2              | 1               |
| Nasopharyngitis                         |                |                |                 |
| subjects affected / exposed             | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 8 / 10 (80.00%) |
| occurrences (all)                       | 0              | 12             | 18              |
| Onychomycosis                           |                |                |                 |
| subjects affected / exposed             | 0 / 4 (0.00%)  | 2 / 5 (40.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                       | 0              | 3              | 0               |
| Oral herpes                             |                |                |                 |
| subjects affected / exposed             | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 1 / 10 (10.00%) |
| occurrences (all)                       | 0              | 1              | 3               |
| Osteomyelitis                           |                |                |                 |
| subjects affected / exposed             | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                       | 0              | 1              | 0               |
| Otitis externa                          |                |                |                 |
| subjects affected / exposed             | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 2 / 10 (20.00%) |
| occurrences (all)                       | 0              | 1              | 4               |
| Otitis media                            |                |                |                 |
| subjects affected / exposed             | 1 / 4 (25.00%) | 2 / 5 (40.00%) | 5 / 10 (50.00%) |
| occurrences (all)                       | 1              | 4              | 32              |
| Otitis media acute                      |                |                |                 |
| subjects affected / exposed             | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 1 / 10 (10.00%) |
| occurrences (all)                       | 0              | 1              | 1               |

|                                   |                |                |                 |
|-----------------------------------|----------------|----------------|-----------------|
| Otitis media chronic              |                |                |                 |
| subjects affected / exposed       | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                 | 0              | 0              | 1               |
| Lice infestation                  |                |                |                 |
| subjects affected / exposed       | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 1 / 10 (10.00%) |
| occurrences (all)                 | 0              | 1              | 1               |
| Scarlet fever                     |                |                |                 |
| subjects affected / exposed       | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                 | 0              | 1              | 0               |
| Rhinovirus infection              |                |                |                 |
| subjects affected / exposed       | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 3 / 10 (30.00%) |
| occurrences (all)                 | 0              | 0              | 4               |
| Skin candida                      |                |                |                 |
| subjects affected / exposed       | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                 | 0              | 0              | 1               |
| Skin infection                    |                |                |                 |
| subjects affected / exposed       | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                 | 0              | 0              | 1               |
| Subcutaneous abscess              |                |                |                 |
| subjects affected / exposed       | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                 | 0              | 1              | 0               |
| Tinea pedis                       |                |                |                 |
| subjects affected / exposed       | 0 / 4 (0.00%)  | 2 / 5 (40.00%) | 2 / 10 (20.00%) |
| occurrences (all)                 | 0              | 2              | 3               |
| Tooth abscess                     |                |                |                 |
| subjects affected / exposed       | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 2 / 10 (20.00%) |
| occurrences (all)                 | 0              | 2              | 2               |
| Upper respiratory tract infection |                |                |                 |
| subjects affected / exposed       | 3 / 4 (75.00%) | 4 / 5 (80.00%) | 8 / 10 (80.00%) |
| occurrences (all)                 | 3              | 16             | 47              |
| Urinary tract infection           |                |                |                 |
| subjects affected / exposed       | 0 / 4 (0.00%)  | 1 / 5 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                 | 0              | 1              | 0               |
| Pharyngitis                       |                |                |                 |
| subjects affected / exposed       | 0 / 4 (0.00%)  | 0 / 5 (0.00%)  | 2 / 10 (20.00%) |
| occurrences (all)                 | 0              | 0              | 2               |

|                                                                                             |                     |                      |                       |
|---------------------------------------------------------------------------------------------|---------------------|----------------------|-----------------------|
| Pharyngitis streptococcal<br>subjects affected / exposed<br>occurrences (all)               | 0 / 4 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0   | 1 / 10 (10.00%)<br>1  |
| Pneumonia<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 4 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0   | 4 / 10 (40.00%)<br>5  |
| Pneumonia viral<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 4 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0   | 1 / 10 (10.00%)<br>1  |
| Rhinitis<br>subjects affected / exposed<br>occurrences (all)                                | 1 / 4 (25.00%)<br>1 | 3 / 5 (60.00%)<br>15 | 3 / 10 (30.00%)<br>13 |
| Sinusitis<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 4 (0.00%)<br>0  | 1 / 5 (20.00%)<br>1  | 5 / 10 (50.00%)<br>11 |
| Viral upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 0 / 4 (0.00%)<br>0  | 2 / 5 (40.00%)<br>2  | 0 / 10 (0.00%)<br>0   |
| Metabolism and nutrition disorders                                                          |                     |                      |                       |
| Abnormal loss of weight<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 4 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0   | 1 / 10 (10.00%)<br>1  |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 4 (25.00%)<br>1 | 1 / 5 (20.00%)<br>1  | 5 / 10 (50.00%)<br>7  |
| Dehydration<br>subjects affected / exposed<br>occurrences (all)                             | 1 / 4 (25.00%)<br>1 | 0 / 5 (0.00%)<br>0   | 1 / 10 (10.00%)<br>1  |
| Hypoalbuminaemia<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 4 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0   | 1 / 10 (10.00%)<br>2  |
| Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 4 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0   | 1 / 10 (10.00%)<br>1  |
| Hypophagia                                                                                  |                     |                      |                       |

|                             |                |               |                 |
|-----------------------------|----------------|---------------|-----------------|
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 5 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all)           | 0              | 0             | 2               |
| Pica                        |                |               |                 |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%) | 0 / 10 (0.00%)  |
| occurrences (all)           | 2              | 0             | 0               |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

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

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported