



## Clinical trial results:

### An Open-Label Extension Study of Gene-Activated® Human Glucocerebrosidase (GA-GCB) Enzyme Replacement Therapy in Patients with Type 1 Gaucher Disease

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2008-001965-27   |
| Trial protocol           | GB ES            |
| Global end of trial date | 28 December 2012 |

#### Results information

|                                |                   |
|--------------------------------|-------------------|
| Result version number          | v1 (current)      |
| This version publication date  | 04 September 2018 |
| First version publication date | 20 March 2015     |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | HGT-GCB-044 |
|-----------------------|-------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00635427 |
| 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               | MedInfo, Shire, +1 8668880660,<br>US_ShireHGT_Medicalinformation@shire.com |
| Scientific contact           | MedInfo, Shire, +1 8668880660,<br>US_ShireHGT_Medicalinformation@shire.com |

Notes:

##### Paediatric regulatory details

|  |                     |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP)       | Yes                 |
| EMA paediatric investigation plan number(s)                          | EMA-000556-PIP01-09 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No                  |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No                  |

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 28 December 2012 |
| Is this the analysis of the primary completion data? | No               |

|                                  |                  |
|----------------------------------|------------------|
| Global end of trial reached?     | Yes              |
| Global end of trial date         | 28 December 2012 |
| Was the trial ended prematurely? | No               |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this Phase III clinical study was to evaluate the long-term safety of velaglucerase alfa when administered every other week (EOW) intravenously (IV) in subjects with type 1 Gaucher disease.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice (GCP) and applicable regulatory requirements. Known instances of non-conformance were documented and are not considered to have had an impact on the overall conclusions of this study.

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 13 March 2008 |
| 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 Kingdom: 4     |
| Country: Number of subjects enrolled | Tunisia: 9            |
| Country: Number of subjects enrolled | Spain: 4              |
| Country: Number of subjects enrolled | Korea, Republic of: 1 |
| Country: Number of subjects enrolled | Russian Federation: 7 |
| Country: Number of subjects enrolled | Poland: 5             |
| Country: Number of subjects enrolled | Paraguay: 16          |
| Country: Number of subjects enrolled | Israel: 18            |
| Country: Number of subjects enrolled | India: 7              |
| Country: Number of subjects enrolled | United States: 21     |
| Country: Number of subjects enrolled | Argentina: 3          |
| Worldwide total number of subjects   | 95                    |
| EEA total number of subjects         | 13                    |

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)                     | 13 |
| Adolescents (12-17 years)                 | 11 |
| Adults (18-64 years)                      | 68 |
| From 65 to 84 years                       | 3  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

The first subject was enrolled in the study on 13 March 2008 and the last subject completed study procedures on 28 December 2012.

### Pre-assignment

Screening details: -

### Pre-assignment period milestones

|  |                                      |
|--|--------------------------------------|
| Number of subjects started                 | 95                                   |
| Intermediate milestone: Number of subjects | Intent-to-treat (ITT) population: 93 |
| Intermediate milestone: Number of subjects | Safety population: 95                |
| Number of subjects completed               | 93                                   |

### Pre-assignment subject non-completion reasons

|                            |  |
|----------------------------|--|
| Reason: Number of subjects | Did not have type 1 Gaucher disease: 2 |
|----------------------------|--|

### Period 1

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

### Arms

|                              |   |
|------------------------------|---|
| Are arms mutually exclusive? | Yes   |
| <b>Arm title</b>             | VPRIV 60 U/kg (Parent Study VPRIV (45 U/kg)-TKT032) |

Arm description:

VPRIV 45 units per kilogram (U/kg), IV, EOW for 51 weeks in parent study TKT032 (2008-001965-27) and switched to 60 U/kg in HGT-GCB-044.

|  |  |
|--|--|
| Arm type                               | Experimental   |
| Investigational medicinal product name | Velaglucerase alfa                                       |
| Investigational medicinal product code |  |
| Other name                             | VPRIV®, Gene-Activated Human Glucocerebrosidase (GA-GCB) |
| Pharmaceutical forms                   | Infusion   |
| Routes of administration               | Intravenous use  |

Dosage and administration details:

VPRIV 45 U/kg, IV, EOW for 51 weeks in parent study TKT032 (2008-001965-27) and switched to 60 U/kg in HGT-GCB-044.

|                  |   |
|------------------|---|
| <b>Arm title</b> | VPRIV 60 U/kg (Parent Study VPRIV (60 U/kg)-TKT032) |
|------------------|---|

Arm description:

VPRIV 60 U/kg, IV, EOW for 51 weeks in parent study TKT032 (2008-001965-27).

|  |  |
|--|--|
| Arm type                               | Experimental   |
| Investigational medicinal product name | Velaglucerase alfa                                       |
| Investigational medicinal product code |  |
| Other name                             | VPRIV®, Gene-Activated Human Glucocerebrosidase (GA-GCB) |
| Pharmaceutical forms                   | Infusion   |
| Routes of administration               | Intravenous use  |

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**Dosage and administration details:**

VPRIV 60 U/kg, IV, EOW for 51 weeks in parent study TKT032 (2008-001965-27).

|  |  |
|--|--|
| <b>Arm title</b>   | VPRIV 60 U/kg (Parent Study VPRIV (60U/kg) HGT-GCB-039)  |
| Arm description:<br>VPRIV 60 U/kg, IV, EOW for 39 weeks in parent study HGT-GCB-039 (NCT00553631, 2007-002840-21). |  |
| Arm type   | Experimental   |
| Investigational medicinal product name   | Velaglucerase alfa                                       |
| Investigational medicinal product code   |  |
| Other name   | VPRIV®, Gene-Activated Human Glucocerebrosidase (GA-GCB) |
| Pharmaceutical forms   | Infusion   |
| Routes of administration   | Intravenous use  |

**Dosage and administration details:**

VPRIV 60 U/kg, IV, EOW for 39 weeks in parent study HGT-GCB-039 (NCT00553631, 2007-002840-21).

|  |  |
|--|--|
| <b>Arm title</b>   | VPRIV 60 U/kg (Parent Study imiglucerase(60 U/kg) HGT-GCB-039) |
| Arm description:<br>Imiglucerase 60 U/kg, IV, EOW for 39 weeks in parent study HGT-GCB-039 (NCT00553631, 2007-002840-21) and switched to 60 U/kg VPRIV in HGT-GCB-044. |  |
| Arm type   | Experimental   |
| Investigational medicinal product name   | Velaglucerase alfa   |
| Investigational medicinal product code   |  |
| Other name   | VPRIV®, Gene-Activated Human Glucocerebrosidase (GA-GCB)       |
| Pharmaceutical forms   | Infusion   |
| Routes of administration   | Intravenous use  |

**Dosage and administration details:**

Imiglucerase 60 U/kg, IV, EOW for 39 weeks in parent study HGT-GCB-039 (NCT00553631, 2007-002840-21) and switched 60 U/kg VPRIV in HGT-GCB-044.

|  |   |
|--|---|
| <b>Arm title</b>   | VPRIV 15-60 U/kg (Parent Study VPRIV (15-60 U/kg)-TKT034) |
| Arm description:<br>VPRIV 15-60 U/kg, IV, EOW for 51 weeks in parent study TKT034 (NCT00478647, 2006-006304-11) and continued in HGT-GCB-044 at the same dose as prescribed in TKT034. |   |
| Arm type   | Experimental  |
| Investigational medicinal product name   | Velaglucerase alfa  |
| Investigational medicinal product code   |   |
| Other name   | VPRIV®, Gene-Activated Human Glucocerebrosidase (GA-GCB)  |
| Pharmaceutical forms   | Infusion  |
| Routes of administration   | Intravenous use   |

**Dosage and administration details:**

VPRIV 15-60 U/kg, IV, EOW for 51 weeks in parent study TKT034 (NCT00478647, 2006-006304-11) and continued in HGT-GCB-044 at the same dose as prescribed in TKT034.

| Number of subjects in period 1 <sup>[1]</sup> | VPRIV 60 U/kg (Parent Study VPRIV (45 U/kg)-TKT032) | VPRIV 60 U/kg (Parent Study VPRIV (60 U/kg)-TKT032) | VPRIV 60 U/kg (Parent Study VPRIV (60U/kg) HGT-GCB-039) |
|---|---|---|---|
|   |   |   |   |
| Started                                       | 12  | 11  | 16  |
| Completed                                     | 1   | 6   | 5   |
| Not completed                                 | 11  | 5   | 11  |
| Consent withdrawn by subject                  | -   | -   | -   |
| Death   | -   | -   | -   |
| 'Refusal of required diagnostic evaluation '  | -   | -   | 1   |
| Termination of study by sponsor               | 11  | 5   | 10  |

| Number of subjects in period 1 <sup>[1]</sup> | VPRIV 60 U/kg (Parent Study imiglucerase(60 U/kg) HGT-GCB-039) | VPRIV 15-60 U/kg (Parent Study VPRIV (15-60 U/kg)-TKT034) |
|---|--|---|
|   |  |   |
| Started                                       | 16   | 38  |
| Completed                                     | 7  | 30  |
| Not completed                                 | 9  | 8   |
| Consent withdrawn by subject                  | 2  | 2   |
| Death   | 1  | -   |
| 'Refusal of required diagnostic evaluation '  | -  | -   |
| Termination of study by sponsor               | 6  | 6   |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Two subjects who did not have type 1 Gaucher disease were withdrawn from the ITT population as per statistical analysis plan (SAP) definition and removed from the long-term efficacy analyses in this study, needed to support the interpretation of the long-term efficacy results. Hence, 93 of 95 enrolled subjects worldwide were included in the baseline period which consisted of HGT-GCB-044 ITT population.

## Baseline characteristics

### Reporting groups

|  |  |
|--|--|
| Reporting group title  | VPRIV 60 U/kg (Parent Study VPRIV (45 U/kg)-TKT032)            |
| Reporting group description:<br>VPRIV 45 units per kilogram (U/kg), IV, EOW for 51 weeks in parent study TKT032 (2008-001965-27) and switched to 60 U/kg in HGT-GCB-044.                           |  |
| Reporting group title  | VPRIV 60 U/kg (Parent Study VPRIV (60 U/kg)-TKT032)            |
| Reporting group description:<br>VPRIV 60 U/kg, IV, EOW for 51 weeks in parent study TKT032 (2008-001965-27).   |  |
| Reporting group title  | VPRIV 60 U/kg (Parent Study VPRIV (60U/kg) HGT-GCB-039)        |
| Reporting group description:<br>VPRIV 60 U/kg, IV, EOW for 39 weeks in parent study HGT-GCB-039 (NCT00553631, 2007-002840-21).   |  |
| Reporting group title  | VPRIV 60 U/kg (Parent Study imiglucerase(60 U/kg) HGT-GCB-039) |
| Reporting group description:<br>Imiglucerase 60 U/kg, IV, EOW for 39 weeks in parent study HGT-GCB-039 (NCT00553631, 2007-002840-21) and switched to 60 U/kg VPRIV in HGT-GCB-044.                 |  |
| Reporting group title  | VPRIV 15-60 U/kg (Parent Study VPRIV (15-60 U/kg)-TKT034)      |
| Reporting group description:<br>VPRIV 15-60 U/kg, IV, EOW for 51 weeks in parent study TKT034 (NCT00478647, 2006-006304-11) and continued in HGT-GCB-044 at the same dose as prescribed in TKT034. |  |

| Reporting group values   | VPRIV 60 U/kg<br>(Parent Study VPRIV<br>(45 U/kg)-TKT032) | VPRIV 60 U/kg<br>(Parent Study VPRIV<br>(60 U/kg)-TKT032) | VPRIV 60 U/kg<br>(Parent Study VPRIV<br>(60U/kg) HGT-GCB-<br>039) |
|--|---|---|---|
| Number of subjects   | 12  | 11  | 16  |
| Age categorical  |   |   |   |
| ITT population included all enrolled subjects who had type 1 Gaucher disease. Age at the time the informed consent was obtained in the core study. |   |   |   |
| Units: Subjects  |   |   |   |
| At least 18 years  | 2   | 3   | 3   |
| Between 18 and 65 years  | 10  | 8   | 13  |
| Greater than or equal to 65 years  | 0   | 0   | 0   |
| Age continuous   |   |   |   |
| ITT population. Age at the time the informed consent was obtained in the core study.   |   |   |   |
| Units: years   |   |   |   |
| arithmetic mean  | 32.5  | 22  | 32.9  |
| standard deviation   | ± 16.75   | ± 11.08   | ± 16.14   |
| Gender categorical   |   |   |   |
| ITT population.  |   |   |   |
| Units: Subjects  |   |   |   |
| Female   | 7   | 6   | 8   |
| Male   | 5   | 5   | 8   |
| Splenectomy status   |   |   |   |
| ITT population.  |   |   |   |
| Units: Subjects  |   |   |   |
| Yes  | 0   | 0   | 9   |
| No   | 12  | 11  | 7   |

|  |             |             |             |
|--|-------------|-------------|-------------|
| Baseline hemoglobin concentration per treatment group  |             |             |             |
| ITT population. Baseline was defined as data collected prior to the first dose in the core study (TKT032, TKT034, and HGT-GCB-039).  |             |             |             |
| Units: gram per deciliter  |             |             |             |
| arithmetic mean  | 10.68       | 10.68       | 11.56       |
| full range (min-max)   | 8.5 to 12.9 | 7.1 to 12.3 | 9.7 to 14.4 |
| Baseline platelet counts per treatment group   |             |             |             |
| ITT population. Baseline was defined as data collected prior to the first dose in the core study (TKT032, TKT034, and HGT-GCB-039).  |             |             |             |
| Units: x10 <sup>9</sup> /L   |             |             |             |
| arithmetic mean  | 69.3        | 79.4        | 160.1       |
| full range (min-max)   | 13 to 146   | 47 to 139   | 44 to 310   |
| Baseline liver volume per treatment group  |             |             |             |
| ITT population. Baseline was defined as data collected prior to the first dose in the core study (TKT032, TKT034, and HGT-GCB-039). Normal liver volume is defined as 2.5 percent of body weight.    |             |             |             |
| Units: Percent (%) body weight   |             |             |             |
| arithmetic mean  | 1.64        | 1.63        | 1.59        |
| full range (min-max)   | 1.1 to 2.9  | 1 to 3.2    | 0.8 to 2.2  |
| Baseline Spleen volume per treatment group   |             |             |             |
| ITT population. Baseline was defined as data collected prior to the first dose in the core study (TKT032, TKT034, and HT-GCB-039). Normal spleen volume is defined as 0.2 percentage of body weight. |             |             |             |
| Units: Multiple of Normal (MN)   |             |             |             |
| arithmetic mean  | 23.08       | 18.48       | 12.69       |
| full range (min-max)   | 4.8 to 65.1 | 5.7 to 36.9 | 7.2 to 31.6 |

| <b>Reporting group values</b>  | VPRIV 60 U/kg<br>(Parent Study<br>imiglucerase(60<br>U/kg) HGT-GCB-<br>039) | VPRIV 15-60 U/kg<br>(Parent Study VPRIV<br>(15-60 U/kg)-<br>TKT034) | Total |
|--|---|---|-------|
| Number of subjects   | 16  | 38  | 93    |
| Age categorical  |   |   |       |
| ITT population included all enrolled subjects who had type 1 Gaucher disease. Age at the time the informed consent was obtained in the core study. |   |   |       |
| Units: Subjects  |   |   |       |
| At least 18 years  | 5   | 9   | 22    |
| Between 18 and 65 years  | 11  | 26  | 68    |
| Greater than or equal to 65 years  | 0   | 3   | 3     |
| Age continuous   |   |   |       |
| ITT population. Age at the time the informed consent was obtained in the core study.   |   |   |       |
| Units: years   |   |   |       |
| arithmetic mean  | 25  | 34.3  |       |
| standard deviation   | ± 17.33   | ± 17.94   | -     |
| Gender categorical   |   |   |       |
| ITT population.  |   |   |       |
| Units: Subjects  |   |   |       |
| Female   | 7   | 18  | 46    |
| Male   | 9   | 20  | 47    |
| Splenectomy status   |   |   |       |
| ITT population.  |   |   |       |
| Units: Subjects  |   |   |       |
| Yes  | 10  | 3   | 22    |

|    |   |    |    |
|----|---|----|----|
| No | 6 | 35 | 71 |
|----|---|----|----|

|  |             |              |   |
|--|-------------|--------------|---|
| Baseline hemoglobin concentration per treatment group  |             |              |   |
| ITT population. Baseline was defined as data collected prior to the first dose in the core study (TKT032, TKT034, and HGT-GCB-039).  |             |              |   |
| Units: gram per deciliter  |             |              |   |
| arithmetic mean  | 10.58       | 13.82        |   |
| full range (min-max)   | 8.1 to 13.1 | 10.7 to 16.5 | - |
| Baseline platelet counts per treatment group   |             |              |   |
| ITT population. Baseline was defined as data collected prior to the first dose in the core study (TKT032, TKT034, and HGT-GCB-039).  |             |              |   |
| Units: x10 <sup>9</sup> /L   |             |              |   |
| arithmetic mean  | 186.3       | 165.4        |   |
| full range (min-max)   | 63 to 430   | 29 to 399    | - |
| Baseline liver volume per treatment group  |             |              |   |
| ITT population. Baseline was defined as data collected prior to the first dose in the core study (TKT032, TKT034, and HGT-GCB-039). Normal liver volume is defined as 2.5 percent of body weight.    |             |              |   |
| Units: Percent (%) body weight   |             |              |   |
| arithmetic mean  | 1.68        | 0.82         |   |
| full range (min-max)   | 0.7 to 2.8  | 0.6 to 1.3   | - |
| Baseline Spleen volume per treatment group   |             |              |   |
| ITT population. Baseline was defined as data collected prior to the first dose in the core study (TKT032, TKT034, and HT-GCB-039). Normal spleen volume is defined as 0.2 percentage of body weight. |             |              |   |
| Units: Multiple of Normal (MN)   |             |              |   |
| arithmetic mean  | 23.52       | 4.1          |   |
| full range (min-max)   | 3.1 to 44.4 | 1.2 to 15.8  | - |

## End points

### End points reporting groups

|   |  |
|---|--|
| Reporting group title   | VPRIV 60 U/kg (Parent Study VPRIV (45 U/kg)-TKT032)            |
| Reporting group description:<br>VPRIV 45 units per kilogram (U/kg), IV, EOW for 51 weeks in parent study TKT032 (2008-001965-27) and switched to 60 U/kg in HGT-GCB-044.  |  |
| Reporting group title   | VPRIV 60 U/kg (Parent Study VPRIV (60 U/kg)-TKT032)            |
| Reporting group description:<br>VPRIV 60 U/kg, IV, EOW for 51 weeks in parent study TKT032 (2008-001965-27).  |  |
| Reporting group title   | VPRIV 60 U/kg (Parent Study VPRIV (60U/kg) HGT-GCB-039)        |
| Reporting group description:<br>VPRIV 60 U/kg, IV, EOW for 39 weeks in parent study HGT-GCB-039 (NCT00553631, 2007-002840-21).  |  |
| Reporting group title   | VPRIV 60 U/kg (Parent Study imiglucerase(60 U/kg) HGT-GCB-039) |
| Reporting group description:<br>Imiglucerase 60 U/kg, IV, EOW for 39 weeks in parent study HGT-GCB-039 (NCT00553631, 2007-002840-21) and switched to 60 U/kg VPRIV in HGT-GCB-044.  |  |
| Reporting group title   | VPRIV 15-60 U/kg (Parent Study VPRIV (15-60 U/kg)-TKT034)      |
| Reporting group description:<br>VPRIV 15-60 U/kg, IV, EOW for 51 weeks in parent study TKT034 (NCT00478647, 2006-006304-11) and continued in HGT-GCB-044 at the same dose as prescribed in TKT034.  |  |
| Subject analysis set title  | VPRIV 60 U/kg(Parent Study VPRIV(45 or 60 U/kg) TKT032,GCB039) |
| Subject analysis set type   | Safety analysis  |
| Subject analysis set description:<br>This arm is the Overall velaglucerase alfa (VPRIV) 60 U/kg and includes subjects from the following groups:<br>VPRIV 45 U/kg or 60 U/kg, IV, EOW for 51 weeks in parent study TKT032 (2008-001965-27) and switched to 60 U/kg in HGT-GCB-044 to maintain blindness or 60 U/kg, IV, EOW for 39 weeks in parent study HGT-GCB-039 (NCT00553631, 2007-002840-21). |  |

### Primary: Overall Summary of Treatment Emergent Adverse Events (TEAEs)

|   |  |
|---|--|
| End point title   | Overall Summary of Treatment Emergent Adverse Events (TEAEs) <sup>[1][2]</sup> |
| End point description:<br>Safety was evaluated by an analysis of adverse events (AEs), concomitant medication use, clinical laboratory tests, vital signs during the infusion of study drug, physical examination, and the development of anti-velaglucerase alfa. No formal comparisons or statistical tests were applied for the safety analyses, including for differences between the groups. All subjects who received at least 1 infusion (full or partial) of study drug were evaluated for safety (that is, were included in the safety population). There were 95 subjects in the safety population. |  |
| End point type  | Primary  |
| End point timeframe:<br>Baseline to termination of study  |  |

#### 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: Inferential statistical analysis was not planned for this endpoint. Only descriptive statistics were reported.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: A subject analysis set "VPRIV 60 U/kg (Parent Study VPRIV(45 or 60 U/kg) TKT032, GCB039)" was created by combining 3 reporting groups [VPRIV 60 U/kg (Parent Study VPRIV (45 U/kg)-TKT032); VPRIV 60 U/kg (Parent Study VPRIV (60 U/kg)-TKT032); VPRIV 60 U/kg (Parent Study VPRIV (60U/kg) HGT-GCB-039)] of the baseline period and reported statistics for this endpoint as planned.

| End point values                              | VPRIV 60 U/kg (Parent Study imiglucerase(60 U/kg) HGT-GCB-039) | VPRIV 15-60 U/kg (Parent Study VPRIV (15-60 U/kg)-TKT034) | VPRIV 60 U/kg(Parent Study VPRIV(45 or 60 U/kg) |  |
|---|--|---|---|--|
| Subject group type                            | Reporting group  | Reporting group   | Subject analysis set                            |  |
| Number of subjects analysed                   | 16   | 38  | 41  |  |
| Units: Subjects                               |  |   |   |  |
| Experienced no AEs                            | 1  | 3   | 3   |  |
| Experienced at least 1 AE                     | 15   | 35  | 38  |  |
| Experienced at least 1 drug-related (DR) AE   | 7  | 8   | 9   |  |
| Experienced at least 1 infusion-related AE    | 1  | 5   | 5   |  |
| Experienced at least 1 severe AE              | 3  | 4   | 4   |  |
| Experienced at least 1 DR severe AE           | 0  | 0   | 0   |  |
| Experienced at least 1 Life-threatening AE    | 0  | 0   | 0   |  |
| Experienced at least 1 DR Life-threatening AE | 0  | 0   | 0   |  |
| Experienced at least 1 serious AE             | 4  | 6   | 6   |  |
| Experienced at least 1 DR serious AE          | 0  | 0   | 0   |  |
| Discontinued due to an AE                     | 0  | 0   | 0   |  |
| Deaths  | 1  | 0   | 0   |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline to 24 Months in Hemoglobin Concentration for Each Treatment Group

|                        |   |
|------------------------|---|
| End point title        | Change From Baseline to 24 Months in Hemoglobin Concentration for Each Treatment Group <sup>[3]</sup> |
| End point description: | ITT population included all enrolled subjects who had type 1 Gaucher disease.                         |
| End point type         | Secondary   |
| End point timeframe:   |   |
| Baseline to 24 months  |   |

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: A subject analysis set "VPRIV 60 U/kg (Parent Study VPRIV(45 or 60 U/kg) TKT032, GCB039)" was created by combining 3 reporting groups [VPRIV 60 U/kg (Parent Study VPRIV (45 U/kg)-TKT032); VPRIV 60 U/kg (Parent Study VPRIV (60 U/kg)-TKT032); VPRIV 60 U/kg (Parent Study VPRIV (60U/kg) HGT-GCB-039)] of the baseline period and reported statistics for this endpoint as planned.

| End point values                      | VPRIV 60 U/kg (Parent Study imiglucerase(60 U/kg) HGT-GCB-039) | VPRIV 15-60 U/kg (Parent Study VPRIV (15-60 U/kg)-TKT034) | VPRIV 60 U/kg(Parent Study VPRIV(45 or 60 U/kg) |  |
|---------------------------------------|--|---|---|--|
| Subject group type                    | Reporting group  | Reporting group   | Subject analysis set                            |  |
| Number of subjects analysed           | 16   | 38  | 39  |  |
| Units: gram per deciliter             |  |   |   |  |
| arithmetic mean (confidence interval) | 2 (1.25 to   | -0.05 (-0.34 to   | 2.75 (2.28 to                                   |  |

|      |       |       |       |
|------|-------|-------|-------|
| 95%) | 2.75) | 0.25) | 3.22) |
|------|-------|-------|-------|

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline to 24 Months in Platelet Counts for Each Treatment Group

|   |  |
|---|--|
| End point title                               | Change From Baseline to 24 Months in Platelet Counts for Each Treatment Group <sup>[4]</sup> |
| End point description:<br>ITT population.     |  |
| End point type                                | Secondary  |
| End point timeframe:<br>Baseline to 24 months |  |

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: A subject analysis set "VPRIV 60 U/kg (Parent Study VPRIV(45 or 60 U/kg) TKT032, GCB039)" was created by combining 3 reporting groups [VPRIV 60 U/kg (Parent Study VPRIV (45 U/kg)-TKT032); VPRIV 60 U/kg (Parent Study VPRIV (60 U/kg)-TKT032); VPRIV 60 U/kg (Parent Study VPRIV (60U/kg) HGT-GCB-039)] of the baseline period and reported statistics for this endpoint as planned.

| End point values                          | VPRIV 60 U/kg (Parent Study imiglucerase(60 U/kg) HGT-GCB-039) | VPRIV 15-60 U/kg (Parent Study VPRIV (15-60 U/kg)-TKT034) | VPRIV 60 U/kg(Parent Study VPRIV(45 or 60 U/kg) |  |
|---|--|---|---|--|
| Subject group type                        | Reporting group  | Reporting group   | Subject analysis set                            |  |
| Number of subjects analysed               | 16   | 38  | 39  |  |
| Units: 10 <sup>9</sup> per liter          |  |   |   |  |
| arithmetic mean (confidence interval 95%) | 160.94 (117.22 to 204.66)                                      | 9.03 (-2.6 to 20.66)                                      | 87.85 (72.69 to 103)                            |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline to 24 Months in Normalized Liver Volume for Each Treatment Group

|   |  |
|---|--|
| End point title                               | Change From Baseline to 24 Months in Normalized Liver Volume for Each Treatment Group <sup>[5]</sup> |
| End point description:<br>ITT population.     |  |
| End point type                                | Secondary  |
| End point timeframe:<br>Baseline to 24 months |  |

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: A subject analysis set "VPRIV 60 U/kg (Parent Study VPRIV(45 or 60 U/kg) TKT032, GCB039)" was created by combining 3 reporting groups [VPRIV 60 U/kg (Parent Study VPRIV (45 U/kg)-TKT032); VPRIV 60 U/kg (Parent Study VPRIV (60 U/kg)-TKT032); VPRIV 60 U/kg (Parent Study VPRIV (60U/kg) HGT-GCB-039)] of the baseline period and reported statistics for this endpoint as planned.

| End point values                          | VPRIV 60 U/kg (Parent Study imiglucerase(60 U/kg) HGT-GCB-039) | VPRIV 15-60 U/kg (Parent Study VPRIV (15-60 U/kg)-TKT034) | VPRIV 60 U/kg(Parent Study VPRIV(45 or 60 U/kg) |  |
|---|--|---|---|--|
| Subject group type                        | Reporting group  | Reporting group   | Subject analysis set                            |  |
| Number of subjects analysed               | 16   | 38  | 39  |  |
| Units: Percent (%) Body weight            |  |   |   |  |
| arithmetic mean (confidence interval 95%) | -1.688 (-2.164 to -1.211)                                      | -0.026 (-0.1 to 0.047)                                    | -1.206 (-1.501 to -0.912)                       |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage Change From Baseline to 24 Months in Normalized Spleen Volume for Each Treatment Group

|                        |  |
|------------------------|--|
| End point title        | Percentage Change From Baseline to 24 Months in Normalized Spleen Volume for Each Treatment Group <sup>[6]</sup> |
| End point description: |  |
| ITT population.        |  |
| End point type         | Secondary  |
| End point timeframe:   |  |
| Baseline to 24 months  |  |

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: A subject analysis set "VPRIV 60 U/kg (Parent Study VPRIV(45 or 60 U/kg) TKT032, GCB039)" was created by combining 3 reporting groups [VPRIV 60 U/kg (Parent Study VPRIV (45 U/kg)-TKT032); VPRIV 60 U/kg (Parent Study VPRIV (60 U/kg)-TKT032); VPRIV 60 U/kg (Parent Study VPRIV (60U/kg) HGT-GCB-039)] of the baseline period and reported statistics for this endpoint as planned.

| End point values                          | VPRIV 60 U/kg (Parent Study imiglucerase(60 U/kg) HGT-GCB-039) | VPRIV 15-60 U/kg (Parent Study VPRIV (15-60 U/kg)-TKT034) | VPRIV 60 U/kg(Parent Study VPRIV(45 or 60 U/kg) |  |
|---|--|---|---|--|
| Subject group type                        | Reporting group  | Reporting group   | Subject analysis set                            |  |
| Number of subjects analysed               | 16   | 38  | 39  |  |
| Units: Percent (%) change                 |  |   |   |  |
| arithmetic mean (confidence interval 95%) | -63.82 (-89.65 to -37.98)                                      | -8.04 (-14 to -2.08)                                      | -64.49 (-69.26 to -59.73)                       |  |

## Statistical analyses



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

TEAEs were defined as AEs which occurred on or after the time of the first infusion in HGT-GCB-044, until 30 days after the subject's last study infusion

Adverse event reporting additional description:

AEs may have been discovered through observation or examination of the subject, questioning of the subject, complaint by the subject, or by an abnormal clinical laboratory value. Severity of AEs was to be assessed by the investigator and recorded on the electronic case report form regardless of the severity or relationship to study drug.

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

### Dictionary used

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

|                    |     |
|--------------------|-----|
| Dictionary version | 9.0 |
|--------------------|-----|

### Reporting groups

|                       |   |
|-----------------------|---|
| Reporting group title | VPRIV 15-60 U/kg (Parent Study VPRIV (15-60 U/kg) TKT034) |
|-----------------------|---|

Reporting group description:

VPRIV 15-60 U/kg, IV, EOW for 51 weeks in parent study TKT034 (NCT00478647, 2006-006304-11) and continued in HGT-GCB-044 at the same dose as prescribed in TKT034.

|                       |  |
|-----------------------|--|
| Reporting group title | VPRIV 60 U/kg (Parent Study-imiglucerase(60 U/kg) HGT-GCB-039) |
|-----------------------|--|

Reporting group description:

Imiglucerase 60 U/kg, IV, EOW for 39 weeks in parent study HGT-GCB-039 (NCT00553631, 2007-002840-21) and switched to 60 U/kg VPRIV in HGT-GCB-044.

|                       |   |
|-----------------------|---|
| Reporting group title | VPRIV 60 U/kg(VPRIV Parent Study 45 or 60 U/kg-TKT032,GCB039) |
|-----------------------|---|

Reporting group description:

This arm is the Overall velaglucerase alfa (VPRIV) 60 U/kg and includes subjects from the following groups:

VPRIV 45 U/kg or 60 U/kg, IV, EOW for 51 weeks in parent study TKT032 (2008-001965-27) and switched to 60 U/kg in HGT-GCB-044 to maintain blindness or 60 U/kg, IV, EOW for 39 weeks in parent study HGT-GCB-039 (NCT00553631, 2007-002840-21).

| Serious adverse events  | VPRIV 15-60 U/kg<br>(Parent Study VPRIV<br>(15-60 U/kg)<br>TKT034) | VPRIV 60 U/kg<br>(Parent Study-<br>imiglucerase(60<br>U/kg) HGT-GCB-<br>039) | VPRIV 60<br>U/kg(VPRIV Parent<br>Study 45 or 60<br>U/kg- |
|---|--|--|--|
| Total subjects affected by serious adverse events                   |  |  |  |
| subjects affected / exposed   | 6 / 38 (15.79%)  | 4 / 16 (25.00%)  | 6 / 41 (14.63%)  |
| number of deaths (all causes)                                       | 0  | 1  | 0  |
| number of deaths resulting from adverse events                      |  |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |  |  |  |
| Benign renal neoplasm   |  |  |  |
| subjects affected / exposed   | 0 / 38 (0.00%)   | 0 / 16 (0.00%)   | 1 / 41 (2.44%)   |
| occurrences causally related to treatment / all                     | 0 / 0  | 0 / 0  | 0 / 1  |
| deaths causally related to treatment / all                          | 0 / 0  | 0 / 0  | 0 / 0  |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Injury, poisoning and procedural complications  |                |                |                |
| Lower limb fracture                             |                |                |                |
| subjects affected / exposed                     | 0 / 38 (0.00%) | 0 / 16 (0.00%) | 1 / 41 (2.44%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Post procedural haematoma                       |                |                |                |
| subjects affected / exposed                     | 1 / 38 (2.63%) | 0 / 16 (0.00%) | 0 / 41 (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          |
| Vascular disorders                              |                |                |                |
| Phlebitis                                       |                |                |                |
| subjects affected / exposed                     | 1 / 38 (2.63%) | 0 / 16 (0.00%) | 0 / 41 (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          |
| Nervous system disorders                        |                |                |                |
| Convulsion                                      |                |                |                |
| subjects affected / exposed                     | 0 / 38 (0.00%) | 1 / 16 (6.25%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| Syncope   |                |                |                |
| subjects affected / exposed                     | 1 / 38 (2.63%) | 0 / 16 (0.00%) | 0 / 41 (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          |
| Pregnancy, puerperium and perinatal conditions  |                |                |                |
| Abortion  |                |                |                |
| subjects affected / exposed                     | 0 / 38 (0.00%) | 0 / 16 (0.00%) | 1 / 41 (2.44%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Oligohydramnios                                 |                |                |                |
| subjects affected / exposed                     | 1 / 38 (2.63%) | 0 / 16 (0.00%) | 0 / 41 (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          |
| Blood and lymphatic system disorders            |                |                |                |
| Splenomegaly                                    |                |                |                |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                          | 1 / 38 (2.63%) | 0 / 16 (0.00%) | 0 / 41 (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          |
| General disorders and administration site conditions |                |                |                |
| Non-Cardiac chest pain                               |                |                |                |
| subjects affected / exposed                          | 0 / 38 (0.00%) | 0 / 16 (0.00%) | 1 / 41 (2.44%) |
| 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 hernia                                     |                |                |                |
| subjects affected / exposed                          | 1 / 38 (2.63%) | 0 / 16 (0.00%) | 0 / 41 (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          |
| Umbilical hernia                                     |                |                |                |
| subjects affected / exposed                          | 0 / 38 (0.00%) | 1 / 16 (6.25%) | 0 / 41 (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          |
| Hepatobiliary disorders                              |                |                |                |
| Cholelithiasis                                       |                |                |                |
| subjects affected / exposed                          | 0 / 38 (0.00%) | 1 / 16 (6.25%) | 1 / 41 (2.44%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                          |                |                |                |
| Renal colic  |                |                |                |
| subjects affected / exposed                          | 0 / 38 (0.00%) | 0 / 16 (0.00%) | 1 / 41 (2.44%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Musculoskeletal and connective tissue disorders      |                |                |                |
| Arthralgia   |                |                |                |
| subjects affected / exposed                          | 1 / 38 (2.63%) | 0 / 16 (0.00%) | 1 / 41 (2.44%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Lumbar spinal stenosis                               |                |                |                |

|   |                |                 |                |
|---|----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 38 (2.63%) | 0 / 16 (0.00%)  | 0 / 41 (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          |
| Osteonecrosis                                   |                |                 |                |
| subjects affected / exposed                     | 0 / 38 (0.00%) | 2 / 16 (12.50%) | 2 / 41 (4.88%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3           | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Infections and infestations                     |                |                 |                |
| Bronchopneumonia                                |                |                 |                |
| subjects affected / exposed                     | 0 / 38 (0.00%) | 1 / 16 (6.25%)  | 0 / 41 (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          |
| Pyelonephritis acute                            |                |                 |                |
| subjects affected / exposed                     | 0 / 38 (0.00%) | 0 / 16 (0.00%)  | 1 / 41 (2.44%) |
| 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 tract infection                     |                |                 |                |
| subjects affected / exposed                     | 0 / 38 (0.00%) | 1 / 16 (6.25%)  | 0 / 41 (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          |
| Urinary tract infection                         |                |                 |                |
| subjects affected / exposed                     | 1 / 38 (2.63%) | 0 / 16 (0.00%)  | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0           | 0 / 0          |
| 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>                                   | VPRIV 15-60 U/kg<br>(Parent Study VPRIV<br>(15-60 U/kg)<br>TKT034) | VPRIV 60 U/kg<br>(Parent Study-<br>imiglucerase(60<br>U/kg) HGT-GCB-<br>039) | VPRIV 60<br>U/kg(VPRIV Parent<br>Study 45 or 60<br>U/kg- |
|---|--|--|--|
| Total subjects affected by non-serious adverse events               |  |  |  |
| subjects affected / exposed   | 35 / 38 (92.11%)   | 15 / 16 (93.75%)   | 35 / 41 (85.37%)   |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |  |  |  |

|  |                      |                     |                       |
|--|----------------------|---------------------|-----------------------|
| Lentigo<br>subjects affected / exposed<br>occurrences (all)  | 0 / 38 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1 | 0 / 41 (0.00%)<br>0   |
| Vascular disorders<br>Haematoma<br>subjects affected / exposed<br>occurrences (all)  | 2 / 38 (5.26%)<br>2  | 0 / 16 (0.00%)<br>0 | 1 / 41 (2.44%)<br>1   |
| Hypertension<br>subjects affected / exposed<br>occurrences (all)   | 4 / 38 (10.53%)<br>6 | 0 / 16 (0.00%)<br>0 | 5 / 41 (12.20%)<br>6  |
| General disorders and administration<br>site conditions<br>Adverse drug reaction<br>subjects affected / exposed<br>occurrences (all) | 2 / 38 (5.26%)<br>2  | 0 / 16 (0.00%)<br>0 | 0 / 41 (0.00%)<br>0   |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)  | 7 / 38 (18.42%)<br>8 | 0 / 16 (0.00%)<br>0 | 3 / 41 (7.32%)<br>3   |
| Chest discomfort<br>subjects affected / exposed<br>occurrences (all)   | 0 / 38 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1 | 0 / 41 (0.00%)<br>0   |
| Gait disturbance<br>subjects affected / exposed<br>occurrences (all)   | 0 / 38 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1 | 0 / 41 (0.00%)<br>0   |
| Influenza like illness<br>subjects affected / exposed<br>occurrences (all)   | 2 / 38 (5.26%)<br>3  | 0 / 16 (0.00%)<br>0 | 0 / 41 (0.00%)<br>0   |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)  | 2 / 38 (5.26%)<br>2  | 1 / 16 (6.25%)<br>1 | 6 / 41 (14.63%)<br>10 |
| Reproductive system and breast<br>disorders<br>Galactorrhoea<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 38 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1 | 0 / 41 (0.00%)<br>0   |
| Respiratory, thoracic and mediastinal<br>disorders   |                      |                     |                       |

|                                      |                 |                 |                |
|--------------------------------------|-----------------|-----------------|----------------|
| Cough                                |                 |                 |                |
| subjects affected / exposed          | 5 / 38 (13.16%) | 3 / 16 (18.75%) | 0 / 41 (0.00%) |
| occurrences (all)                    | 6               | 4               | 0              |
| Dysphonia                            |                 |                 |                |
| subjects affected / exposed          | 2 / 38 (5.26%)  | 0 / 16 (0.00%)  | 0 / 41 (0.00%) |
| occurrences (all)                    | 2               | 0               | 0              |
| Epistaxis                            |                 |                 |                |
| subjects affected / exposed          | 1 / 38 (2.63%)  | 1 / 16 (6.25%)  | 0 / 41 (0.00%) |
| occurrences (all)                    | 2               | 1               | 0              |
| Dyspnoea                             |                 |                 |                |
| subjects affected / exposed          | 1 / 38 (2.63%)  | 1 / 16 (6.25%)  | 0 / 41 (0.00%) |
| occurrences (all)                    | 2               | 3               | 0              |
| Pharyngolaryngeal pain               |                 |                 |                |
| subjects affected / exposed          | 5 / 38 (13.16%) | 0 / 16 (0.00%)  | 3 / 41 (7.32%) |
| occurrences (all)                    | 8               | 0               | 4              |
| Postnasal drip                       |                 |                 |                |
| subjects affected / exposed          | 2 / 38 (5.26%)  | 0 / 16 (0.00%)  | 0 / 41 (0.00%) |
| occurrences (all)                    | 2               | 0               | 0              |
| Productive cough                     |                 |                 |                |
| subjects affected / exposed          | 0 / 38 (0.00%)  | 0 / 16 (0.00%)  | 4 / 41 (9.76%) |
| occurrences (all)                    | 0               | 0               | 5              |
| Rhinitis allergic                    |                 |                 |                |
| subjects affected / exposed          | 0 / 38 (0.00%)  | 1 / 16 (6.25%)  | 1 / 41 (2.44%) |
| occurrences (all)                    | 0               | 3               | 1              |
| Sinus congestion                     |                 |                 |                |
| subjects affected / exposed          | 3 / 38 (7.89%)  | 0 / 16 (0.00%)  | 0 / 41 (0.00%) |
| occurrences (all)                    | 3               | 0               | 0              |
| Tachypnoea                           |                 |                 |                |
| subjects affected / exposed          | 0 / 38 (0.00%)  | 1 / 16 (6.25%)  | 0 / 41 (0.00%) |
| occurrences (all)                    | 0               | 2               | 0              |
| Investigations                       |                 |                 |                |
| Alanine aminotransferase increased   |                 |                 |                |
| subjects affected / exposed          | 2 / 38 (5.26%)  | 1 / 16 (6.25%)  | 0 / 41 (0.00%) |
| occurrences (all)                    | 2               | 1               | 0              |
| Aspartate aminotransferase increased |                 |                 |                |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                    | 1 / 38 (2.63%) | 1 / 16 (6.25%) | 0 / 41 (0.00%) |
| occurrences (all)                              | 1              | 1              | 0              |
| Blood creatine phosphokinase increased         |                |                |                |
| subjects affected / exposed                    | 2 / 38 (5.26%) | 0 / 16 (0.00%) | 1 / 41 (2.44%) |
| occurrences (all)                              | 2              | 0              | 3              |
| Blood urine present                            |                |                |                |
| subjects affected / exposed                    | 0 / 38 (0.00%) | 1 / 16 (6.25%) | 1 / 41 (2.44%) |
| occurrences (all)                              | 0              | 1              | 1              |
| Haemoglobin decreased                          |                |                |                |
| subjects affected / exposed                    | 0 / 38 (0.00%) | 1 / 16 (6.25%) | 0 / 41 (0.00%) |
| occurrences (all)                              | 0              | 1              | 0              |
| Mean cell volume increased                     |                |                |                |
| subjects affected / exposed                    | 0 / 38 (0.00%) | 1 / 16 (6.25%) | 0 / 41 (0.00%) |
| occurrences (all)                              | 0              | 1              | 0              |
| Neutrophil count increased                     |                |                |                |
| subjects affected / exposed                    | 0 / 38 (0.00%) | 1 / 16 (6.25%) | 0 / 41 (0.00%) |
| occurrences (all)                              | 0              | 1              | 0              |
| Red blood cell count decreased                 |                |                |                |
| subjects affected / exposed                    | 0 / 38 (0.00%) | 1 / 16 (6.25%) | 0 / 41 (0.00%) |
| occurrences (all)                              | 0              | 1              | 0              |
| Red blood cells urine positive                 |                |                |                |
| subjects affected / exposed                    | 0 / 38 (0.00%) | 1 / 16 (6.25%) | 1 / 41 (2.44%) |
| occurrences (all)                              | 0              | 1              | 1              |
| White blood cell count increased               |                |                |                |
| subjects affected / exposed                    | 0 / 38 (0.00%) | 1 / 16 (6.25%) | 0 / 41 (0.00%) |
| occurrences (all)                              | 0              | 1              | 0              |
| White blood cells urine positive               |                |                |                |
| subjects affected / exposed                    | 2 / 38 (5.26%) | 1 / 16 (6.25%) | 0 / 41 (0.00%) |
| occurrences (all)                              | 2              | 1              | 0              |
| Injury, poisoning and procedural complications |                |                |                |
| Anaemia postoperative                          |                |                |                |
| subjects affected / exposed                    | 0 / 38 (0.00%) | 1 / 16 (6.25%) | 1 / 41 (2.44%) |
| occurrences (all)                              | 0              | 1              | 1              |
| Burns first degree                             |                |                |                |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 38 (0.00%)  | 0 / 16 (0.00%)  | 3 / 41 (7.32%)  |
| occurrences (all)           | 0               | 0               | 5               |
| Contusion                   |                 |                 |                 |
| subjects affected / exposed | 1 / 38 (2.63%)  | 1 / 16 (6.25%)  | 0 / 41 (0.00%)  |
| occurrences (all)           | 2               | 1               | 0               |
| Excoriation                 |                 |                 |                 |
| subjects affected / exposed | 1 / 38 (2.63%)  | 1 / 16 (6.25%)  | 0 / 41 (0.00%)  |
| occurrences (all)           | 1               | 1               | 0               |
| Injury                      |                 |                 |                 |
| subjects affected / exposed | 0 / 38 (0.00%)  | 1 / 16 (6.25%)  | 2 / 41 (4.88%)  |
| occurrences (all)           | 0               | 1               | 2               |
| Joint injury                |                 |                 |                 |
| subjects affected / exposed | 0 / 38 (0.00%)  | 1 / 16 (6.25%)  | 0 / 41 (0.00%)  |
| occurrences (all)           | 0               | 1               | 0               |
| Muscle strain               |                 |                 |                 |
| subjects affected / exposed | 2 / 38 (5.26%)  | 0 / 16 (0.00%)  | 0 / 41 (0.00%)  |
| occurrences (all)           | 2               | 0               | 0               |
| Procedural pain             |                 |                 |                 |
| subjects affected / exposed | 3 / 38 (7.89%)  | 0 / 16 (0.00%)  | 0 / 41 (0.00%)  |
| occurrences (all)           | 6               | 0               | 0               |
| Skin laceration             |                 |                 |                 |
| subjects affected / exposed | 0 / 38 (0.00%)  | 1 / 16 (6.25%)  | 0 / 41 (0.00%)  |
| occurrences (all)           | 0               | 1               | 0               |
| Nervous system disorders    |                 |                 |                 |
| Convulsion                  |                 |                 |                 |
| subjects affected / exposed | 0 / 38 (0.00%)  | 1 / 16 (6.25%)  | 0 / 41 (0.00%)  |
| occurrences (all)           | 0               | 1               | 0               |
| Dizziness                   |                 |                 |                 |
| subjects affected / exposed | 0 / 38 (0.00%)  | 1 / 16 (6.25%)  | 3 / 41 (7.32%)  |
| occurrences (all)           | 0               | 3               | 3               |
| Drop attacks                |                 |                 |                 |
| subjects affected / exposed | 0 / 38 (0.00%)  | 1 / 16 (6.25%)  | 0 / 41 (0.00%)  |
| occurrences (all)           | 0               | 1               | 0               |
| Headache                    |                 |                 |                 |
| subjects affected / exposed | 6 / 38 (15.79%) | 4 / 16 (25.00%) | 7 / 41 (17.07%) |
| occurrences (all)           | 10              | 6               | 16              |

|   |                     |                     |                     |
|---|---------------------|---------------------|---------------------|
| Hypoaesthesia<br>subjects affected / exposed<br>occurrences (all)           | 0 / 38 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1 | 0 / 41 (0.00%)<br>0 |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)            | 2 / 38 (5.26%)<br>2 | 1 / 16 (6.25%)<br>3 | 2 / 41 (4.88%)<br>2 |
| Sciatica<br>subjects affected / exposed<br>occurrences (all)                | 0 / 38 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1 | 0 / 41 (0.00%)<br>0 |
| Blood and lymphatic system disorders  |                     |                     |                     |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 38 (2.63%)<br>1 | 1 / 16 (6.25%)<br>2 | 0 / 41 (0.00%)<br>0 |
| Leukocytosis<br>subjects affected / exposed<br>occurrences (all)            | 0 / 38 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1 | 0 / 41 (0.00%)<br>0 |
| Lymphadenitis<br>subjects affected / exposed<br>occurrences (all)           | 0 / 38 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1 | 0 / 41 (0.00%)<br>0 |
| Splenomegaly<br>subjects affected / exposed<br>occurrences (all)            | 0 / 38 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 3 / 41 (7.32%)<br>3 |
| Eye disorders   |                     |                     |                     |
| Conjunctivitis allergic<br>subjects affected / exposed<br>occurrences (all) | 0 / 38 (0.00%)<br>0 | 1 / 16 (6.25%)<br>2 | 0 / 41 (0.00%)<br>0 |
| Dry eye<br>subjects affected / exposed<br>occurrences (all)                 | 2 / 38 (5.26%)<br>2 | 0 / 16 (0.00%)<br>0 | 0 / 41 (0.00%)<br>0 |
| Visual acuity reduced<br>subjects affected / exposed<br>occurrences (all)   | 0 / 38 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1 | 1 / 41 (2.44%)<br>1 |
| Gastrointestinal disorders  |                     |                     |                     |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)          | 2 / 38 (5.26%)<br>2 | 1 / 16 (6.25%)<br>1 | 3 / 41 (7.32%)<br>3 |
| Abdominal pain upper  |                     |                     |                     |

|  |                |                 |                 |
|--|----------------|-----------------|-----------------|
| subjects affected / exposed            | 3 / 38 (7.89%) | 2 / 16 (12.50%) | 4 / 41 (9.76%)  |
| occurrences (all)                      | 4              | 2               | 6               |
| Diarrhoea                              |                |                 |                 |
| subjects affected / exposed            | 2 / 38 (5.26%) | 1 / 16 (6.25%)  | 2 / 41 (4.88%)  |
| occurrences (all)                      | 2              | 1               | 3               |
| Dyspepsia                              |                |                 |                 |
| subjects affected / exposed            | 2 / 38 (5.26%) | 0 / 16 (0.00%)  | 3 / 41 (7.32%)  |
| occurrences (all)                      | 4              | 0               | 3               |
| Rectal haemorrhage                     |                |                 |                 |
| subjects affected / exposed            | 1 / 38 (2.63%) | 1 / 16 (6.25%)  | 0 / 41 (0.00%)  |
| occurrences (all)                      | 1              | 1               | 0               |
| Toothache                              |                |                 |                 |
| subjects affected / exposed            | 2 / 38 (5.26%) | 2 / 16 (12.50%) | 6 / 41 (14.63%) |
| occurrences (all)                      | 3              | 2               | 7               |
| Vomiting                               |                |                 |                 |
| subjects affected / exposed            | 2 / 38 (5.26%) | 0 / 16 (0.00%)  | 1 / 41 (2.44%)  |
| occurrences (all)                      | 2              | 0               | 1               |
| Hepatobiliary disorders                |                |                 |                 |
| Biliary colic                          |                |                 |                 |
| subjects affected / exposed            | 0 / 38 (0.00%) | 1 / 16 (6.25%)  | 0 / 41 (0.00%)  |
| occurrences (all)                      | 0              | 2               | 0               |
| Cholelithiasis                         |                |                 |                 |
| subjects affected / exposed            | 0 / 38 (0.00%) | 2 / 16 (12.50%) | 0 / 41 (0.00%)  |
| occurrences (all)                      | 0              | 2               | 0               |
| Cytolytic hepatitis                    |                |                 |                 |
| subjects affected / exposed            | 0 / 38 (0.00%) | 0 / 16 (0.00%)  | 3 / 41 (7.32%)  |
| occurrences (all)                      | 0              | 0               | 6               |
| Liver disorder                         |                |                 |                 |
| subjects affected / exposed            | 0 / 38 (0.00%) | 1 / 16 (6.25%)  | 0 / 41 (0.00%)  |
| occurrences (all)                      | 0              | 1               | 0               |
| Skin and subcutaneous tissue disorders |                |                 |                 |
| Dermatitis allergic                    |                |                 |                 |
| subjects affected / exposed            | 2 / 38 (5.26%) | 0 / 16 (0.00%)  | 0 / 41 (0.00%)  |
| occurrences (all)                      | 2              | 0               | 0               |
| Dermatitis contact                     |                |                 |                 |

|   |                 |                 |                  |
|---|-----------------|-----------------|------------------|
| subjects affected / exposed                     | 0 / 38 (0.00%)  | 1 / 16 (6.25%)  | 0 / 41 (0.00%)   |
| occurrences (all)                               | 0               | 1               | 0                |
| Erythema  |                 |                 |                  |
| subjects affected / exposed                     | 0 / 38 (0.00%)  | 1 / 16 (6.25%)  | 0 / 41 (0.00%)   |
| occurrences (all)                               | 0               | 1               | 0                |
| Rash vesicular                                  |                 |                 |                  |
| subjects affected / exposed                     | 0 / 38 (0.00%)  | 1 / 16 (6.25%)  | 0 / 41 (0.00%)   |
| occurrences (all)                               | 0               | 7               | 0                |
| Pruritus generalised                            |                 |                 |                  |
| subjects affected / exposed                     | 1 / 38 (2.63%)  | 1 / 16 (6.25%)  | 0 / 41 (0.00%)   |
| occurrences (all)                               | 1               | 1               | 0                |
| Renal and urinary disorders                     |                 |                 |                  |
| Nephrolithiasis                                 |                 |                 |                  |
| subjects affected / exposed                     | 0 / 38 (0.00%)  | 1 / 16 (6.25%)  | 0 / 41 (0.00%)   |
| occurrences (all)                               | 0               | 1               | 0                |
| Endocrine disorders                             |                 |                 |                  |
| Hyperprolactinaemia                             |                 |                 |                  |
| subjects affected / exposed                     | 0 / 38 (0.00%)  | 1 / 16 (6.25%)  | 0 / 41 (0.00%)   |
| occurrences (all)                               | 0               | 1               | 0                |
| Musculoskeletal and connective tissue disorders |                 |                 |                  |
| Arthralgia                                      |                 |                 |                  |
| subjects affected / exposed                     | 9 / 38 (23.68%) | 2 / 16 (12.50%) | 14 / 41 (34.15%) |
| occurrences (all)                               | 13              | 34              | 33               |
| Arthritis                                       |                 |                 |                  |
| subjects affected / exposed                     | 1 / 38 (2.63%)  | 2 / 16 (12.50%) | 0 / 41 (0.00%)   |
| occurrences (all)                               | 1               | 2               | 0                |
| Back pain                                       |                 |                 |                  |
| subjects affected / exposed                     | 4 / 38 (10.53%) | 1 / 16 (6.25%)  | 5 / 41 (12.20%)  |
| occurrences (all)                               | 7               | 1               | 6                |
| Bone pain                                       |                 |                 |                  |
| subjects affected / exposed                     | 7 / 38 (18.42%) | 2 / 16 (12.50%) | 7 / 41 (17.07%)  |
| occurrences (all)                               | 12              | 7               | 20               |
| Myalgia   |                 |                 |                  |
| subjects affected / exposed                     | 2 / 38 (5.26%)  | 0 / 16 (0.00%)  | 3 / 41 (7.32%)   |
| occurrences (all)                               | 3               | 0               | 3                |
| Muscle spasms                                   |                 |                 |                  |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 38 (0.00%)  | 1 / 16 (6.25%)  | 0 / 41 (0.00%)  |
| occurrences (all)           | 0               | 1               | 0               |
| Osteoarthritis              |                 |                 |                 |
| subjects affected / exposed | 3 / 38 (7.89%)  | 0 / 16 (0.00%)  | 1 / 41 (2.44%)  |
| occurrences (all)           | 3               | 0               | 1               |
| Pain in extremity           |                 |                 |                 |
| subjects affected / exposed | 4 / 38 (10.53%) | 1 / 16 (6.25%)  | 5 / 41 (12.20%) |
| occurrences (all)           | 6               | 1               | 6               |
| Shoulder pain               |                 |                 |                 |
| subjects affected / exposed | 3 / 38 (7.89%)  | 1 / 16 (6.25%)  | 2 / 41 (4.88%)  |
| occurrences (all)           | 4               | 2               | 4               |
| Infections and infestations |                 |                 |                 |
| Bronchitis                  |                 |                 |                 |
| subjects affected / exposed | 1 / 38 (2.63%)  | 1 / 16 (6.25%)  | 5 / 41 (12.20%) |
| occurrences (all)           | 1               | 1               | 13              |
| Bronchitis acute            |                 |                 |                 |
| subjects affected / exposed | 0 / 38 (0.00%)  | 1 / 16 (6.25%)  | 5 / 41 (12.20%) |
| occurrences (all)           | 0               | 1               | 5               |
| Dental caries               |                 |                 |                 |
| subjects affected / exposed | 0 / 38 (0.00%)  | 1 / 16 (6.25%)  | 1 / 41 (2.44%)  |
| occurrences (all)           | 0               | 1               | 1               |
| Diarrhoea infectious        |                 |                 |                 |
| subjects affected / exposed | 2 / 38 (5.26%)  | 0 / 16 (0.00%)  | 0 / 41 (0.00%)  |
| occurrences (all)           | 2               | 0               | 0               |
| Gastroenteritis             |                 |                 |                 |
| subjects affected / exposed | 2 / 38 (5.26%)  | 1 / 16 (6.25%)  | 7 / 41 (17.07%) |
| occurrences (all)           | 2               | 1               | 10              |
| Hepatitis a                 |                 |                 |                 |
| subjects affected / exposed | 0 / 38 (0.00%)  | 1 / 16 (6.25%)  | 0 / 41 (0.00%)  |
| occurrences (all)           | 0               | 1               | 0               |
| Hordeolum                   |                 |                 |                 |
| subjects affected / exposed | 1 / 38 (2.63%)  | 1 / 16 (6.25%)  | 2 / 41 (4.88%)  |
| occurrences (all)           | 1               | 1               | 3               |
| Influenza                   |                 |                 |                 |
| subjects affected / exposed | 4 / 38 (10.53%) | 4 / 16 (25.00%) | 6 / 41 (14.63%) |
| occurrences (all)           | 6               | 12              | 10              |

|                                   |                  |                 |                  |
|-----------------------------------|------------------|-----------------|------------------|
| Nasopharyngitis                   |                  |                 |                  |
| subjects affected / exposed       | 16 / 38 (42.11%) | 3 / 16 (18.75%) | 11 / 41 (26.83%) |
| occurrences (all)                 | 31               | 4               | 20               |
| Lower respiratory tract infection |                  |                 |                  |
| subjects affected / exposed       | 0 / 38 (0.00%)   | 1 / 16 (6.25%)  | 0 / 41 (0.00%)   |
| occurrences (all)                 | 0                | 1               | 0                |
| Pharyngitis                       |                  |                 |                  |
| subjects affected / exposed       | 5 / 38 (13.16%)  | 1 / 16 (6.25%)  | 2 / 41 (4.88%)   |
| occurrences (all)                 | 11               | 1               | 2                |
| Pyelonephritis acute              |                  |                 |                  |
| subjects affected / exposed       | 0 / 38 (0.00%)   | 1 / 16 (6.25%)  | 0 / 41 (0.00%)   |
| occurrences (all)                 | 0                | 1               | 0                |
| Respiratory tract infection       |                  |                 |                  |
| subjects affected / exposed       | 1 / 38 (2.63%)   | 2 / 16 (12.50%) | 0 / 41 (0.00%)   |
| occurrences (all)                 | 2                | 3               | 0                |
| Rhinitis                          |                  |                 |                  |
| subjects affected / exposed       | 0 / 38 (0.00%)   | 1 / 16 (6.25%)  | 3 / 41 (7.32%)   |
| occurrences (all)                 | 0                | 1               | 3                |
| Sinusitis                         |                  |                 |                  |
| subjects affected / exposed       | 3 / 38 (7.89%)   | 0 / 16 (0.00%)  | 0 / 41 (0.00%)   |
| occurrences (all)                 | 5                | 0               | 0                |
| Tinea versicolour                 |                  |                 |                  |
| subjects affected / exposed       | 0 / 38 (0.00%)   | 1 / 16 (6.25%)  | 4 / 41 (9.76%)   |
| occurrences (all)                 | 0                | 2               | 13               |
| Staphylococcal infection          |                  |                 |                  |
| subjects affected / exposed       | 0 / 38 (0.00%)   | 1 / 16 (6.25%)  | 0 / 41 (0.00%)   |
| occurrences (all)                 | 0                | 1               | 0                |
| Tonsillitis                       |                  |                 |                  |
| subjects affected / exposed       | 1 / 38 (2.63%)   | 0 / 16 (0.00%)  | 4 / 41 (9.76%)   |
| occurrences (all)                 | 1                | 0               | 4                |
| Upper respiratory tract infection |                  |                 |                  |
| subjects affected / exposed       | 9 / 38 (23.68%)  | 6 / 16 (37.50%) | 4 / 41 (9.76%)   |
| occurrences (all)                 | 9                | 14              | 7                |
| Urinary tract infection           |                  |                 |                  |
| subjects affected / exposed       | 3 / 38 (7.89%)   | 0 / 16 (0.00%)  | 3 / 41 (7.32%)   |
| occurrences (all)                 | 5                | 0               | 5                |

|                                |                |                |                |
|--------------------------------|----------------|----------------|----------------|
| Vaginal infection              |                |                |                |
| subjects affected / exposed    | 3 / 38 (7.89%) | 0 / 16 (0.00%) | 1 / 41 (2.44%) |
| occurrences (all)              | 3              | 0              | 1              |
| Varicella                      |                |                |                |
| subjects affected / exposed    | 0 / 38 (0.00%) | 1 / 16 (6.25%) | 0 / 41 (0.00%) |
| occurrences (all)              | 0              | 1              | 0              |
| Vulvovaginal mycotic infection |                |                |                |
| subjects affected / exposed    | 2 / 38 (5.26%) | 0 / 16 (0.00%) | 1 / 41 (2.44%) |
| occurrences (all)              | 2              | 0              | 1              |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment   |
|-----------------|---|
| 09 October 2008 | Amendment 1 was revised from the original version to update the background information and contact information for serious adverse event reporting, and included several clarifications. The major clarification was that subjects completing TKT034 were permitted to continue to receive home infusions or were able to begin home infusions at any time. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported