



Clinical trial results:

An Open-Label Extension of Study TKT024 Evaluating Long-Term Safety and Clinical Outcomes in MPS II Patients Receiving Iduronate-2-Sulfatase Enzyme Replacement Therapy

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2004-002743-27 |
| Trial protocol | DE GB SE IT ES |
| Global end of trial date | 31 January 2008 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 04 September 2018 |
| First version publication date | 25 April 2015 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | TKT024EXT |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00630747 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Shire Human Genetic Therapies |
| Sponsor organisation address | 700 Main Street, Cambridge, Massachusetts, United States, 02139 |
| Public contact | Dr. Arian Pano, Medical Director, Shire Human Genetic Therapies, +1 781-482-0875, apano@shire.com |
| Scientific contact | Dr. Arian Pano, Medical Director, Shire Human Genetic Therapies, +1 781-482-0875, apano@shire.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-000294-PIP02-12 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |
| 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 | 31 January 2008 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|-----------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 31 January 2008 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this open-label extension study was to collect long-term safety and clinical outcome data in subjects with Mucopolysaccharidosis Type II (MPS II) or Hunter Syndrome who were receiving idursulfase (DRX006A) enzyme replacement therapy.

Protection of trial subjects:

This study was conducted in accordance with local regulatory requirements, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and the ethical principles described in the current revision (2002) of Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 13 September 2004 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects**Subjects enrolled per country**

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 22 |
| Country: Number of subjects enrolled | Germany: 18 |
| Country: Number of subjects enrolled | Brazil: 20 |
| Country: Number of subjects enrolled | United States: 34 |
| Worldwide total number of subjects | 94 |
| EEA total number of subjects | 40 |

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) | 34 |
| Adolescents (12-17 years) | 27 |
| Adults (18-64 years) | 33 |

| | |
|---------------------|---|
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

TKT024EXT was designed to allow subjects in the double-blind phase of Study TKT024, a one year Phase 2/Phase 3 registration study, to continue long-term idursulfase therapy and to allow placebo subjects in TKT024 to receive active idursulfase treatment. The first subject enrolled on 13 Sep 2004. The study was conducted at 52 sites in 17 countries

Pre-assignment

Screening details:

Subjects were screened for entry based on their known medical histories and previous participation in the TKT024 study. Subjects had to have completed Week 53 final evaluations in the TKT024 study. Subjects were not to have received any treatment with an investigational therapy other than idursulfase within 60 days of study entry.

Period 1

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

Arms

| | |
|------------------|--|
| Arm title | Idursulfase (0.5 mg/kg, IV, Once-weekly) |
|------------------|--|

Arm description:

Idursulfase 0.5 milligram per kilogram (mg/kg) administered by intravenous (IV) infusion once-weekly.

| | |
|--|----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Idursulfase |
| Investigational medicinal product code | DRX006A |
| Other name | Elaprase®, iduronate-2-sulfatase |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Idursulfase 0.5 mg/kg administered by IV infusion once-weekly.

| Number of subjects in period 1 | Idursulfase (0.5 mg/kg, IV, Once-weekly) |
|--------------------------------------|--|
| Started | 94 |
| Subjects Treated in Phase I of Study | 94 |
| Completed | 85 |
| Not completed | 9 |
| Transferred to Study TKT031NPU | 7 |
| Death | 1 |
| 'Returned to country of origin ' | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Idursulfase (0.5 mg/kg, IV, Once-weekly) |
|-----------------------|--|

Reporting group description:

Idursulfase 0.5 milligram per kilogram (mg/kg) administered by intravenous (IV) infusion once-weekly.

| Reporting group values | Idursulfase (0.5 mg/kg, IV, Once-weekly) | Total | |
|--|--|-------|--|
| Number of subjects | 94 | 94 | |
| Age categorical Units: Subjects | | | |
| ≤18 years | 70 | 70 | |
| Between 18 and 65 years | 24 | 24 | |
| ≥65 years | 0 | 0 | |
| Age continuous Units: years | | | |
| arithmetic mean | 14.52 | | |
| standard deviation | ± 6.634 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 0 | 0 | |
| Male | 94 | 94 | |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 15 | 15 | |
| Not Hispanic or Latino | 79 | 79 | |
| Unknown or Not Reported | 0 | 0 | |
| Race Units: Subjects | | | |
| American Indian or Alaska Native | 3 | 3 | |
| Asian | 5 | 5 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Black or African American | 6 | 6 | |
| White | 78 | 78 | |
| More than one race | 0 | 0 | |
| Unknown or Not Reported | 2 | 2 | |
| Baseline Percent Predicted Forced Vital Capacity (FVC) Units: percent predicted FVC | | | |
| arithmetic mean | 56.16 | | |
| standard deviation | ± 14.897 | - | |
| Baseline Distance Walked in the 6-minute Walk Test (6MWT) Units: meters (m) | | | |
| arithmetic mean | 400.3 | | |
| standard deviation | ± 100.25 | - | |
| Baseline Passive Joint Range of Motion | | | |

| | | | |
|--|-----------|---|--|
| (JROM) | | | |
| Global JROM (percentage (%) normal range of motion) is the average of 11 ratios multiplied by 100. Ratios are Left/Right means of passive range of motion in Shoulder (Flexion/Extension, Abduction, Internal/External Rotation), Elbow (Flexion/Extension), Wrist (Flexion/Extension), Index Finger (Flexion/Extension [Combined MCP, PIP, DIP motion]), Hip (Flexion/Extension, Abduction, Internal/External Rotation), Knee (Flexion/Extension), and Ankle (Dorsiflexion) divided by the normal range (American Academy of Orthopedic Surgeons and American Medical Association). | | | |
| Units: percentage | | | |
| arithmetic mean | 67.44 | | |
| standard deviation | ± 9.042 | - | |
| Baseline Combined Liver and Spleen Volume | | | |
| Units: cubic centimeters (cc) | | | |
| arithmetic mean | 1504.8 | | |
| standard deviation | ± 417.21 | - | |
| Baseline Normalized Urine Glycosaminoglycans (GAG) Levels | | | |
| Units: microgram(mcg)GAG/mg creatinine | | | |
| arithmetic mean | 361.96 | | |
| standard deviation | ± 136.132 | - | |
| Baseline Cardiac Left Ventricular Mass Index (LVMI) | | | |
| Units: Gram per meter ² (g/m ²) | | | |
| arithmetic mean | 97.64 | | |
| standard deviation | ± 36.606 | - | |

End points

End points reporting groups

| | |
|---|--|
| Reporting group title | Idursulfase (0.5 mg/kg, IV, Once-weekly) |
| Reporting group description: Idursulfase 0.5 milligram per kilogram (mg/kg) administered by intravenous (IV) infusion once-weekly. | |

Primary: Change From Baseline in Mean Percent Predicted Forced Vital Capacity (FVC) at Week 105

| | |
|-----------------|---|
| End point title | Change From Baseline in Mean Percent Predicted Forced Vital Capacity (FVC) at Week 105 ^[1] |
|-----------------|---|

End point description:

Determined by spirometry. The change was calculated as Week 105 minus baseline.

All subjects for whom percent predicted FVC were recorded at baseline and at Week 105.

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

End point timeframe:

Baseline and at Week 105

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: Descriptive statistical analysis was only performed and inferential statistical analysis was not performed for this endpoint.

| End point values | Idursulfase (0.5 mg/kg, IV, Once-weekly) | | | |
|----------------------------------|--|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 85 | | | |
| Units: percent predicted FVC | | | | |
| arithmetic mean (standard error) | -0.056 (\pm 1.059) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Mean Distance Walked in the 6-minute Walk Test (6MWT) at Week 105

| | |
|-----------------|--|
| End point title | Change From Baseline in Mean Distance Walked in the 6-minute Walk Test (6MWT) at Week 105 ^[2] |
|-----------------|--|

End point description:

Determined on a walking course. The change was calculated as Week 105 minus baseline.

All subjects for whom distance walked was recorded at baseline and at Week 105.

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

End point timeframe:

Baseline and at Week 105

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: Descriptive statistical analysis was only performed and inferential statistical analysis was not performed for this endpoint.

| | | | | |
|----------------------------------|--|--|--|--|
| End point values | Idursulfase (0.5 mg/kg, IV, Once-weekly) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 85 | | | |
| Units: meters | | | | |
| arithmetic mean (standard error) | 23 (\pm 7.94) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Mean Passive Joint Range of Motion (JROM) at Week 105

| | |
|-----------------|---|
| End point title | Change From Baseline in Mean Passive Joint Range of Motion (JROM) at Week 105 |
|-----------------|---|

End point description:

Change was calculated as Week 105 minus baseline. Global JROM (% normal range of motion) is the average of 11 ratios multiplied by 100. Ratios are Left/Right means of passive range of motion in Shoulder (Flexion/Extension, Abduction, Internal/External Rotation), Elbow (Flexion/Extension), Wrist (Flexion/Extension), Index Finger (Flexion/Extension [Combined Metacarpophalangeal joint (MCP), Proximal interphalangeal joint (PIP), Distal interphalangeal joint (DIP) motion]), Hip (Flexion/Extension, Abduction, Internal/External Rotation), Knee (Flexion/Extension), and Ankle (Dorsiflexion) divided by the normal range (American Academy of Orthopedic Surgeons and American Medical Association).

All subjects for whom passive JROM were recorded at baseline and at Week 105.

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

End point timeframe:

Baseline and at Week 105

| | | | | |
|----------------------------------|--|--|--|--|
| End point values | Idursulfase (0.5 mg/kg, IV, Once-weekly) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 84 | | | |
| Units: percentage | | | | |
| arithmetic mean (standard error) | 0.63 (\pm 0.64) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Mean Combined Liver and Spleen Volume at Week 105

| | |
|-----------------|---|
| End point title | Change From Baseline in Mean Combined Liver and Spleen Volume at Week 105 |
|-----------------|---|

End point description:

Determined by Magnetic Resonance Imaging (MRI). The change was calculated as Week 105 minus baseline.

All subjects for whom combined liver and spleen volume were recorded at baseline and at Week 105.

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

End point timeframe:

Baseline and at Week 105

| | | | | |
|----------------------------------|--|--|--|--|
| End point values | Idursulfase (0.5 mg/kg, IV, Once-weekly) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 79 | | | |
| Units: cubic centimeters | | | | |
| arithmetic mean (standard error) | -325.5 (± 36.84) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Mean Normalized Urine Glycosaminoglycans (GAG) Levels at Week 105

| | |
|-----------------|---|
| End point title | Change From Baseline in Mean Normalized Urine Glycosaminoglycans (GAG) Levels at Week 105 |
|-----------------|---|

End point description:

Determined by urine testing. The change was calculated as Week 105 minus baseline.

All subjects for whom normalized urine GAG levels were recorded at baseline and at Week 105.

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

End point timeframe:

Baseline and at Week 105

| | | | | |
|----------------------------------|--|--|--|--|
| End point values | Idursulfase (0.5 mg/kg, IV, Once-weekly) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 87 | | | |
| Units: µg GAG/mg creatinine | | | | |
| arithmetic mean (standard error) | -238.25 (± 13.333) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Mean Cardiac Left Ventricular Mass Index (LVMI) at Week 105

| | |
|-----------------|---|
| End point title | Change From Baseline in Mean Cardiac Left Ventricular Mass Index (LVMI) at Week 105 |
|-----------------|---|

End point description:

Determined by echocardiogram. LVMI indexed to body surface area (g/m²). The change was calculated as Week 105 minus baseline.

All subjects for whom cardiac LVMI were recorded at baseline and at Week 105.

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

End point timeframe:

Baseline and at Week 105

| | | | | |
|----------------------------------|--|--|--|--|
| End point values | Idursulfase (0.5 mg/kg, IV, Once-weekly) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 71 | | | |
| Units: g/m ² | | | | |
| arithmetic mean (standard error) | 3.28 (± 3.826) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were assessed throughout the duration of the TKT024EXT study. Adverse events were monitored from the time the first subject signed the informed consent until approximately 30 days after the last study visit.

Adverse event reporting additional description:

The "Serious Adverse Events" table lists all serious adverse events that occurred during the study regardless of a relationship to the study drug. The "Other Adverse Events" table lists those non-serious adverse events that were determined to be possibly related to the study drug.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 5.1 |

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Idursulfase (0.5 mg/kg, IV, Once-weekly) |
|-----------------------|--|

Reporting group description:

Idursulfase 0.5 mg/kg administered by IV infusion once-weekly.

| Serious adverse events | Idursulfase (0.5 mg/kg, IV, Once-weekly) | | |
|---|--|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 38 / 94 (40.43%) | | |
| number of deaths (all causes) | 1 | | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Neurilemmoma | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Poor venous access | | | |
| subjects affected / exposed | 10 / 94 (10.64%) | | |
| occurrences causally related to treatment / all | 1 / 10 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Catheter related complication | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hernia nos | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Asthma aggravated | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Foreign body aspiration | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Obstructive airways disorder nos | | | |
| subjects affected / exposed | 2 / 94 (2.13%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Tracheal stenosis | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory distress | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Psychosomatic disease | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Airway complication of anaesthesia | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin laceration | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Arrhythmia nos | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pericardial effusion | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Left ventricular failure | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Carpal tunnel syndrome | | | |
| subjects affected / exposed | 7 / 94 (7.45%) | | |
| occurrences causally related to treatment / all | 0 / 7 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hydrocephalus | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Headache | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal cord compression nos | | | |
| subjects affected / exposed | 3 / 94 (3.19%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ear and labyrinth disorders | | | |
| Tympanic membrane disorder nos | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Gastrointestinal disorders | | | |
| Abdominal pain nos | | | |
| subjects affected / exposed | 2 / 94 (2.13%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal hernia nos | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Appendicitis | | | |
| subjects affected / exposed | 2 / 94 (2.13%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal strangulated hernia | | | |
| subjects affected / exposed | 2 / 94 (2.13%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea nos | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Inguinal hernia nos | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Umbilical hernia nos | | | |
| subjects affected / exposed | 3 / 94 (3.19%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting nos | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|----------------|--|--|
| Rash macular | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Acquired claw toe | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteonecrosis | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Joint contracture | | | |
| subjects affected / exposed | 2 / 94 (2.13%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain in foot | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Bacteraemia | | | |
| subjects affected / exposed | 3 / 94 (3.19%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchopneumonia nos | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocarditis bacterial nos | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lobar pneumonia nos | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Otitis media nos | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Otitis media chronic nos | | | |
| subjects affected / exposed | 2 / 94 (2.13%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Otitis media serous nos | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Otitis media serous chronic nos | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia nos | | | |
| subjects affected / exposed | 3 / 94 (3.19%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper respiratory tract infection nos | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Soft tissue infection nos | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Idursulfase (0.5 mg/kg, IV, Once-weekly) | | |
|---|--|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 94 / 94 (100.00%) | | |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 9 / 94 (9.57%) | | |
| occurrences (all) | 32 | | |
| Pallor | | | |
| subjects affected / exposed | 8 / 94 (8.51%) | | |
| occurrences (all) | 8 | | |
| Hypotension nos | | | |
| subjects affected / exposed | 6 / 94 (6.38%) | | |
| occurrences (all) | 7 | | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 9 / 94 (9.57%) | | |
| occurrences (all) | 19 | | |
| Catheter site pain | | | |
| subjects affected / exposed | 5 / 94 (5.32%) | | |
| occurrences (all) | 5 | | |
| Fall | | | |
| subjects affected / exposed | 12 / 94 (12.77%) | | |
| occurrences (all) | 19 | | |
| Fatigue | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 12 / 94 (12.77%) | | |
| occurrences (all) | 22 | | |
| Influenza like illness | | | |
| subjects affected / exposed | 11 / 94 (11.70%) | | |
| occurrences (all) | 33 | | |
| Gait abnormal | | | |
| subjects affected / exposed | 7 / 94 (7.45%) | | |
| occurrences (all) | 8 | | |
| Injection site extravasation | | | |
| subjects affected / exposed | 6 / 94 (6.38%) | | |
| occurrences (all) | 8 | | |
| Malaise | | | |
| subjects affected / exposed | 7 / 94 (7.45%) | | |
| occurrences (all) | 12 | | |
| Pain nos | | | |
| subjects affected / exposed | 9 / 94 (9.57%) | | |
| occurrences (all) | 16 | | |
| Pyrexia | | | |
| subjects affected / exposed | 57 / 94 (60.64%) | | |
| occurrences (all) | 187 | | |
| Rigors | | | |
| subjects affected / exposed | 11 / 94 (11.70%) | | |
| occurrences (all) | 17 | | |
| Immune system disorders | | | |
| Seasonal allergy | | | |
| subjects affected / exposed | 6 / 94 (6.38%) | | |
| occurrences (all) | 10 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchitis nos | | | |
| subjects affected / exposed | 6 / 94 (6.38%) | | |
| occurrences (all) | 7 | | |
| Asthma nos | | | |
| subjects affected / exposed | 6 / 94 (6.38%) | | |
| occurrences (all) | 7 | | |
| Bronchospasm nos | | | |

| | | | |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 8 / 94 (8.51%) | | |
| occurrences (all) | 19 | | |
| Cough | | | |
| subjects affected / exposed | 53 / 94 (56.38%) | | |
| occurrences (all) | 155 | | |
| Dyspnoea nos | | | |
| subjects affected / exposed | 14 / 94 (14.89%) | | |
| occurrences (all) | 24 | | |
| Nasal congestion | | | |
| subjects affected / exposed | 38 / 94 (40.43%) | | |
| occurrences (all) | 100 | | |
| Epistaxis | | | |
| subjects affected / exposed | 8 / 94 (8.51%) | | |
| occurrences (all) | 23 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 46 / 94 (48.94%) | | |
| occurrences (all) | 102 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 39 / 94 (41.49%) | | |
| occurrences (all) | 84 | | |
| Rhinitis allergic nos | | | |
| subjects affected / exposed | 7 / 94 (7.45%) | | |
| occurrences (all) | 9 | | |
| Productive cough | | | |
| subjects affected / exposed | 7 / 94 (7.45%) | | |
| occurrences (all) | 11 | | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 31 / 94 (32.98%) | | |
| occurrences (all) | 70 | | |
| Rhinitis nos | | | |
| subjects affected / exposed | 14 / 94 (14.89%) | | |
| occurrences (all) | 20 | | |
| Rhonchi | | | |
| subjects affected / exposed | 5 / 94 (5.32%) | | |
| occurrences (all) | 6 | | |
| Sneezing | | | |

| | | | |
|--|------------------------|--|--|
| subjects affected / exposed occurrences (all) | 6 / 94 (6.38%) 7 | | |
| Wheezing subjects affected / exposed occurrences (all) | 15 / 94 (15.96%) 28 | | |
| Investigations Neutrophil count decreased subjects affected / exposed occurrences (all) | 8 / 94 (8.51%) 8 | | |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 5 / 94 (5.32%) 6 | | |
| Injury, poisoning and procedural complications Arthropod bite subjects affected / exposed occurrences (all) | 9 / 94 (9.57%) 11 | | |
| Abrasion nos subjects affected / exposed occurrences (all) | 17 / 94 (18.09%) 24 | | |
| Limb injury nos subjects affected / exposed occurrences (all) | 7 / 94 (7.45%) 9 | | |
| Head injury subjects affected / exposed occurrences (all) | 9 / 94 (9.57%) 9 | | |
| Post procedural pain subjects affected / exposed occurrences (all) | 15 / 94 (15.96%) 25 | | |
| Thermal burn subjects affected / exposed occurrences (all) | 5 / 94 (5.32%) 6 | | |
| Cardiac disorders Atrioventricular block first degree subjects affected / exposed occurrences (all) | 8 / 94 (8.51%) 9 | | |
| Dilatation atrial | | | |

| | | | |
|---|-------------------------|--|--|
| subjects affected / exposed occurrences (all) | 5 / 94 (5.32%) 6 | | |
| Tachycardia nos subjects affected / exposed occurrences (all) | 8 / 94 (8.51%) 24 | | |
| Ventricular hypertrophy subjects affected / exposed occurrences (all) | 6 / 94 (6.38%) 6 | | |
| Nervous system disorders | | | |
| Dizziness subjects affected / exposed occurrences (all) | 18 / 94 (19.15%) 27 | | |
| Carpal tunnel syndrome subjects affected / exposed occurrences (all) | 19 / 94 (20.21%) 20 | | |
| Headache subjects affected / exposed occurrences (all) | 53 / 94 (56.38%) 296 | | |
| Hypoaesthesia subjects affected / exposed occurrences (all) | 8 / 94 (8.51%) 11 | | |
| Insomnia subjects affected / exposed occurrences (all) | 5 / 94 (5.32%) 6 | | |
| Migraine nos subjects affected / exposed occurrences (all) | 5 / 94 (5.32%) 6 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia nos subjects affected / exposed occurrences (all) | 5 / 94 (5.32%) 5 | | |
| Ear and labyrinth disorders | | | |
| Cerumen impaction subjects affected / exposed occurrences (all) | 13 / 94 (13.83%) 17 | | |
| Ear pain | | | |

| | | | |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 24 / 94 (25.53%) | | |
| occurrences (all) | 34 | | |
| Ear haemorrhage | | | |
| subjects affected / exposed | 5 / 94 (5.32%) | | |
| occurrences (all) | 5 | | |
| Otorrhoea | | | |
| subjects affected / exposed | 27 / 94 (28.72%) | | |
| occurrences (all) | 88 | | |
| Eye disorders | | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 5 / 94 (5.32%) | | |
| occurrences (all) | 5 | | |
| Visual acuity reduced | | | |
| subjects affected / exposed | 5 / 94 (5.32%) | | |
| occurrences (all) | 5 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain nos | | | |
| subjects affected / exposed | 34 / 94 (36.17%) | | |
| occurrences (all) | 73 | | |
| Constipation | | | |
| subjects affected / exposed | 11 / 94 (11.70%) | | |
| occurrences (all) | 15 | | |
| Diarrhoea nos | | | |
| subjects affected / exposed | 32 / 94 (34.04%) | | |
| occurrences (all) | 78 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 7 / 94 (7.45%) | | |
| occurrences (all) | 19 | | |
| Flatulence | | | |
| subjects affected / exposed | 5 / 94 (5.32%) | | |
| occurrences (all) | 5 | | |
| Gastroenteritis nos | | | |
| subjects affected / exposed | 10 / 94 (10.64%) | | |
| occurrences (all) | 12 | | |
| Loose stools | | | |

| | | | |
|--|------------------|--|--|
| subjects affected / exposed | 5 / 94 (5.32%) | | |
| occurrences (all) | 5 | | |
| Nausea | | | |
| subjects affected / exposed | 24 / 94 (25.53%) | | |
| occurrences (all) | 44 | | |
| Toothache | | | |
| subjects affected / exposed | 7 / 94 (7.45%) | | |
| occurrences (all) | 9 | | |
| Umbilical hernia nos | | | |
| subjects affected / exposed | 5 / 94 (5.32%) | | |
| occurrences (all) | 5 | | |
| Vomiting nos | | | |
| subjects affected / exposed | 39 / 94 (41.49%) | | |
| occurrences (all) | 102 | | |
| Hepatobiliary disorders | | | |
| Hepatomegaly | | | |
| subjects affected / exposed | 5 / 94 (5.32%) | | |
| occurrences (all) | 5 | | |
| Skin and subcutaneous tissue disorders | | | |
| Acne nos | | | |
| subjects affected / exposed | 14 / 94 (14.89%) | | |
| occurrences (all) | 17 | | |
| Eczema | | | |
| subjects affected / exposed | 7 / 94 (7.45%) | | |
| occurrences (all) | 9 | | |
| Contusion | | | |
| subjects affected / exposed | 9 / 94 (9.57%) | | |
| occurrences (all) | 10 | | |
| Erythema | | | |
| subjects affected / exposed | 11 / 94 (11.70%) | | |
| occurrences (all) | 35 | | |
| Rash macular | | | |
| subjects affected / exposed | 6 / 94 (6.38%) | | |
| occurrences (all) | 11 | | |
| Pruritus | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 11 / 94 (11.70%) | | |
| occurrences (all) | 27 | | |
| Rash nos | | | |
| subjects affected / exposed | 20 / 94 (21.28%) | | |
| occurrences (all) | 60 | | |
| Rash papular | | | |
| subjects affected / exposed | 6 / 94 (6.38%) | | |
| occurrences (all) | 8 | | |
| Skin lesion nos | | | |
| subjects affected / exposed | 9 / 94 (9.57%) | | |
| occurrences (all) | 13 | | |
| Rash pruritic | | | |
| subjects affected / exposed | 10 / 94 (10.64%) | | |
| occurrences (all) | 16 | | |
| Urticaria nos | | | |
| subjects affected / exposed | 14 / 94 (14.89%) | | |
| occurrences (all) | 54 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 39 / 94 (41.49%) | | |
| occurrences (all) | 81 | | |
| Back pain | | | |
| subjects affected / exposed | 23 / 94 (24.47%) | | |
| occurrences (all) | 39 | | |
| Musculoskeletal stiffness | | | |
| subjects affected / exposed | 5 / 94 (5.32%) | | |
| occurrences (all) | 7 | | |
| Myalgia | | | |
| subjects affected / exposed | 11 / 94 (11.70%) | | |
| occurrences (all) | 13 | | |
| Neck pain | | | |
| subjects affected / exposed | 17 / 94 (18.09%) | | |
| occurrences (all) | 24 | | |
| Pain in foot | | | |

| | | | |
|---------------------------------------|------------------|--|--|
| subjects affected / exposed | 5 / 94 (5.32%) | | |
| occurrences (all) | 7 | | |
| Pain in limb | | | |
| subjects affected / exposed | 29 / 94 (30.85%) | | |
| occurrences (all) | 59 | | |
| Infections and infestations | | | |
| Ear infection nos | | | |
| subjects affected / exposed | 36 / 94 (38.30%) | | |
| occurrences (all) | 91 | | |
| Furuncle | | | |
| subjects affected / exposed | 5 / 94 (5.32%) | | |
| occurrences (all) | 5 | | |
| Influenza | | | |
| subjects affected / exposed | 7 / 94 (7.45%) | | |
| occurrences (all) | 11 | | |
| Localised infection | | | |
| subjects affected / exposed | 5 / 94 (5.32%) | | |
| occurrences (all) | 5 | | |
| Lower respiratory tract infection nos | | | |
| subjects affected / exposed | 7 / 94 (7.45%) | | |
| occurrences (all) | 11 | | |
| Otitis media nos | | | |
| subjects affected / exposed | 22 / 94 (23.40%) | | |
| occurrences (all) | 37 | | |
| Otitis media serous nos | | | |
| subjects affected / exposed | 7 / 94 (7.45%) | | |
| occurrences (all) | 9 | | |
| Pneumonia nos | | | |
| subjects affected / exposed | 7 / 94 (7.45%) | | |
| occurrences (all) | 9 | | |
| Respiratory tract infection nos | | | |
| subjects affected / exposed | 6 / 94 (6.38%) | | |
| occurrences (all) | 12 | | |
| Sinusitis nos | | | |
| subjects affected / exposed | 9 / 94 (9.57%) | | |
| occurrences (all) | 16 | | |

| | | | |
|---|------------------|--|--|
| Tinea pedis | | | |
| subjects affected / exposed | 6 / 94 (6.38%) | | |
| occurrences (all) | 21 | | |
| Skin fungal infection nos | | | |
| subjects affected / exposed | 8 / 94 (8.51%) | | |
| occurrences (all) | 9 | | |
| Tonsillitis | | | |
| subjects affected / exposed | 6 / 94 (6.38%) | | |
| occurrences (all) | 6 | | |
| Upper respiratory tract infection nos | | | |
| subjects affected / exposed | 47 / 94 (50.00%) | | |
| occurrences (all) | 106 | | |
| Tooth caries nos | | | |
| subjects affected / exposed | 7 / 94 (7.45%) | | |
| occurrences (all) | 8 | | |
| Upper respiratory tract infection viral nos | | | |
| subjects affected / exposed | 9 / 94 (9.57%) | | |
| occurrences (all) | 13 | | |
| Viral infection nos | | | |
| subjects affected / exposed | 10 / 94 (10.64%) | | |
| occurrences (all) | 12 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 02 September 2004 | Clarified the maintenance of the original blinded treatment assignments in the TKT024 study during the first year of the TKT024EXT study. This change was made to minimize potential bias in evaluation and testing of subjects during the first year of Study TKT024EXT. |
| 26 July 2006 | Changed the study Medical Monitor and the Sponsor's signatory and expanded the visit window for visit 1 from the Week 53 visit of protocol TKT024 to the first visit of protocol TKT024EXT in order to accommodate logistical challenges encountered during the transfer of subjects from main sites to local care sites. |
| 26 July 2006 | Amendment 2 was not processed at the clinical sites, all of these changes were included in amendment 3. Extended the protocol into a second study phase to allow continued treatment after the second year of the study until idursulfase became commercially available and revised safety information presented in the model informed consent based on updated information for Studies TKT024, TKT024EXT, and TKT018. The sponsor's name was changed from Transkaryotic Therapies, Inc. to Shire Human Genetic Therapies, Inc. (Shire HGT). |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

This study design was open-label, and the lack of a concurrently followed placebo group limits the strength of the observations, because the progression of the disease is variable and has not been well described.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/17185020>

<http://www.ncbi.nlm.nih.gov/pubmed/21150784>

<http://www.ncbi.nlm.nih.gov/pubmed/16912578>