



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
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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)
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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)
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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]
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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
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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]
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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
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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
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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
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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
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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
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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
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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
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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/m^2). 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
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Dictionary used

Dictionary name	MedDRA
Dictionary version	5.1

Reporting groups

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

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

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