Clinical trial results:
An Open-label Extension of Study TKT028 Evaluating Safety and Clinical Outcomes of Replagal® Enzyme Replacement Therapy Administered to Adult Patients with Fabry Disease

Summary

EudraCT number	2009-015985-75
Trial protocol	PL CZ GB FI SI
Global end of trial date	08 July 2013

Results information

Result version number	v1 (current)
This version publication date	04 September 2018
First version publication date	07 January 2015

Trial information

Trial identification

Sponsor protocol code	HGT-REP-060

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01124643
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire Human Genetic Therapies
Sponsor organisation address	300 Shire Way, Lexington, MA 02421, United States,
Public contact	Medical Monitor, Shire Human Genetic Therapies, +1 781482-9287, ecrombez@shire.com
Scientific contact	Medical Monitor, Shire Human Genetic Therapies, +1 781482-9287, ecrombez@shire.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 July 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 July 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To evaluate the effect of continued dosing with Replagal (0.2 milligram/kilogram [mg/kg] administered intravenously [IV] every other week [EOW]) following 53 weeks of treatment in Study TKT028 (at 0.2 mg/kg IV every other week or 0.2 mg/kg or 0.4 mg/kg IV every week) on the reduction from baseline in left ventricular mass (LVM) as measured by echocardiography
- To collect long-term safety and clinical outcome data in adult subjects with Fabry disease who are receiving enzyme replacement therapy (ERT) with Replagal

Protection of trial subjects:

The procedures pertaining to the conduct, evaluation, and documentation of this study, were designed to ensure that the Sponsor and Investigators abided by Good Clinical Practice (GCP) as described in the 21 Code of Federal Regulations (CFR) Parts 50, 54, 56, and 312 and the International Conference on Harmonisation (ICH) GCP Guidelines. Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 April 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 13
Country: Number of subjects enrolled	Slovenia: 4
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Czech Republic: 5
Country: Number of subjects enrolled	Finland: 5
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	35
EEA total number of subjects	30

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	32
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Thirty-five of the 40 subjects who completed the parent study (Study TKT028) were enrolled in this extension study.

Period 1

Period 1 title	Replagal® 0.2 mg/kg (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Replagal® 0.2 mg/kg

Arm description:

Replagal® 0.2 mg/kg IV, EOW

Arm type	Experimental
Investigational medicinal product name	Replagal®
Investigational medicinal product code	
Other name	Agalsidase alfa, DRX005B
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Replagal 0.2 mg/kg IV, EOW

Number of subjects in period 1	Replagal® 0.2 mg/kg
Started	35
Completed	34
Not completed	1
Death	1

Baseline characteristics

Reporting groups	
Reporting group title	Replagal® 0.2 mg/kg
Reporting group description:	
Replagal 0.2 mg/kg IV, EOW	

Reporting group values	Replagal® 0.2 mg/kg	Total	
Number of subjects	35	35	
Age categorical			
Age at time of consent			
Units: Subjects			
Between 18 and 65 years	32	32	
>=65 years	3	3	
Age continuous			
Units: years			
arithmetic mean	52.3		
standard deviation	± 9.86	-	
Gender categorical			
Units: Subjects			
Female	16	16	
Male	19	19	
New York Heart Association (NYHA) Functional Class			
Class I: No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea Class II: Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea Class III: Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea Class IV: Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased			
Units: Subjects			
Class I (Very Mild)	21	21	
Class II (Mild)	13	13	
Class III (Moderate)	1	1	
Class IV (Severe)	0	0	
Left Ventricular Mass Indexed to Height (LVMI)			
Number of subjects analyzed for this baseline characteristic was 33			
Units: gram per meter to the power 2.7(g/m^2.7)			
arithmetic mean	81.18		
standard deviation	± 32.13	-	
Maximal Oxygen Consumption (VO2max)			
Number of subjects analyzed for this baseline characteristic was 32			
Units: millilitre/minute/kilogram(mL/min/kg)			
arithmetic mean	20.2		
standard deviation	± 6.73	-	
Distance Walked in 6-Minute Walk Test			

(6MWT)			
Number of subjects analyzed for this baseline characteristic was 34			
Units: meters			
arithmetic mean	515.5		
standard deviation	± 144.13	-	
Minnesota Living with Heart Failure Questionnaire (MLHF-Q) Summary Score			
The MLHF-Q contains 21 questions with answers ranging from 0 (no) to 5 (very much). The final score (0 to 105) is the sum of the points for the 21 questions. A higher score indicates a worse quality of life.			
Units: units on a scale			
arithmetic mean	26.5		
standard deviation	± 26.95	-	
Plasma globotriaosylceramide (Gb3)			
Units: nanomoles per millilitre (nmol/mL)			
arithmetic mean	4.35		
standard deviation	± 2.51	-	
Estimated Glomerular Filtration Rate (eGFR)			
Units: mL/min/1.73m^2			
arithmetic mean	77.6		
standard deviation	± 26.12	-	
Albumin-to-Creatinine (A/Cr) Ratio			
Number of subjects analyzed for this baseline characteristic was 33			
Units: Ratio			
arithmetic mean	284.1		
standard deviation	± 712.9	-	

End points

End points reporting groups

Reporting group title	Replagal® 0.2 mg/kg
Reporting group description:	
Replagal® 0.2 mg/kg IV, EOW	

Primary: Change From Baseline in Left Ventricular Mass Indexed to Height (LVMI)

End point title	Change From Baseline in Left Ventricular Mass Indexed to Height (LVMI)[1]
End point description:	
The Intent-to-Treat (ITT) subject population in this study was defined as all subjects who provided informed consent and received study drug. Subjects who did not have left ventricular hypertrophy were not included in this analysis.	
End point type	Primary
End point timeframe:	
Baseline to 12 months	

Notes:

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

End point values	Replagal® 0.2 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: g/m^2.7				
arithmetic mean (standard deviation)	-0.75 (± 13.46)			

Statistical analyses

No statistical analyses for this end point

Primary: Safety Evaluations

End point title	Safety Evaluations[2]
End point description:	
ITT Population was analysed	
End point type	Primary
End point timeframe:	
Baseline to 12 months	

Notes:

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

End point values	Replagal® 0.2 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Subjects				
No Adverse Event (AE)	3			
At least one AE	32			
At least one study drug-related AE	2			
At least one severe or life-threatening AE	5			
At least one Serious Adverse Event (SAE)	6			
At least one study drug-related SAE	0			
Discontinued due to an AE	1			
Deaths	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Maximal Oxygen Consumption (VO2max) at Peak Exercise

End point title	Change From Baseline in Maximal Oxygen Consumption (VO2max) at Peak Exercise

End point description:

ITT population was analysed. Test was not done or test was not valid for all subjects.

End point type	Secondary

End point timeframe:

Baseline to 12 months

End point values	Replagal® 0.2 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: mL/min/kg				
arithmetic mean (standard deviation)	-0.7 (± 3.11)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Distance Walked in 6- Minute Walk Test (6MWT)

End point title	Change From Baseline in Distance Walked in 6- Minute Walk Test (6MWT)

End point description:

ITT population was analysed. Test was not done or test was not valid for all subjects.

End point type	Secondary

End point timeframe:

Baseline to 12 months

End point values	Replagal® 0.2 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: meters				
arithmetic mean (standard deviation)	-11.2 (± 83.99)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Minnesota Living With Heart Failure Questionnaire (MLHF- Q)

End point title	Change From Baseline in the Minnesota Living With Heart Failure Questionnaire (MLHF- Q)

End point description:

The MLHF-Q contains 21 questions with answers ranging from 0 (no) to 5 (very much). The final score (0 to 105) is the sum of the points for the 21 questions. A higher score indicates a worse quality of life.

ITT population was analysed. Number of subjects analysed signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to 12 months

End point values	Replagal® 0.2 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: units on a scale				
arithmetic mean (standard deviation)	6 (± 19.31)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in New York Heart Association (NYHA) Functional

Class

End point title	Change From Baseline in New York Heart Association (NYHA) Functional Class

End point description:

Class I: No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea
Class II: Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea
Class III: Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea
Class IV: Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.
ITT population was analysed.

End point type	Secondary

End point timeframe:

Baseline to 12 months

End point values	Replagal® 0.2 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Subjects				
Improved >= 1 NYHA Functional Class	0			
Maintained NYHA Functional Class	34			
Missing	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Plasma Gb3

End point title	Change From Baseline in Plasma Gb3

End point description:

ITT population was analysed. Number of subjects analysed signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to 12 months

End point values	Replagal® 0.2 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: nmol/mL				
arithmetic mean (standard deviation)	-1.18 (± 1.52)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in eGFR

End point title	Change From Baseline in eGFR

End point description:

ITT population was analysed. Number of subjects analysed signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to 12 months

End point values	Replagal® 0.2 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: mL/min/1.73m^2				
arithmetic mean (standard deviation)	-3.25 (± 10.22)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Albumin/Creatinine (A/Cr) Ratio

End point title	Change From Baseline in Albumin/Creatinine (A/Cr) Ratio

End point description:

ITT population was analysed. Number of subjects analysed signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to 12 months

End point values	Replagal® 0.2 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: Ratio				
arithmetic mean (standard deviation)	267.6 (± 1247.28)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Baseline to 12 Months	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	12
Reporting groups	
Reporting group title	Replagal® 0.2mg/kg
Reporting group description: Replagal 0.2 mg/kg IV, EOW	

Serious adverse events	Replagal® 0.2mg/kg		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 35 (17.14%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Arteriovenous fistula site complication			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Arteriovenous fistula site haemorrhage			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			

subjects affected / exposed	1 / 35 (2.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Atrial fibrillation				
subjects affected / exposed	2 / 35 (5.71%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	1 / 35 (2.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	1 / 35 (2.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebrovascular accident				
subjects affected / exposed	1 / 35 (2.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Gastritis				
subjects affected / exposed	1 / 35 (2.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Intervertebral disc disorder				
subjects affected / exposed	1 / 35 (2.86%)			
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	Replagal® 0.2mg/kg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 35 (91.43%)		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	4		
Oedema peripheral			
subjects affected / exposed	4 / 35 (11.43%)		
occurrences (all)	4		
Pyrexia			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 35 (14.29%)		
occurrences (all)	8		
Dyspnoea			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	4		
Oropharyngeal pain			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Productive cough			
subjects affected / exposed	4 / 35 (11.43%)		
occurrences (all)	4		
Psychiatric disorders			
Disorientation			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Sleep disorder			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Investigations			
Blood glucose increased			

subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Blood lactate dehydrogenase increased			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	3		
Electrocardiogram QT prolonged			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	3		
Troponin T increased			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	3		
Dilatation atrial			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Left atrial dilatation			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	3		
Palpitations			
subjects affected / exposed	5 / 35 (14.29%)		
occurrences (all)	6		
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 35 (17.14%)		
occurrences (all)	8		
Headache			
subjects affected / exposed	7 / 35 (20.00%)		
occurrences (all)	7		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	3		
Iron deficiency anaemia			

subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Abdominal pain upper			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	7 / 35 (20.00%)		
occurrences (all)	10		
Dyspepsia			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	5 / 35 (14.29%)		
occurrences (all)	12		
Vomiting			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	7		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 35 (11.43%)		
occurrences (all)	5		

Muscle tightness subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2		
Musculoskeletal pain subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 3		
Myalgia subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 3		
Pain in extremity subjects affected / exposed occurrences (all)	6 / 35 (17.14%) 7		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	6 / 35 (17.14%) 7		
Nasopharyngitis subjects affected / exposed occurrences (all)	10 / 35 (28.57%) 15		
Oral herpes subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2		
Respiratory tract infection subjects affected / exposed occurrences (all)	4 / 35 (11.43%) 4		
Urinary tract infection subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 3		
Metabolism and nutrition disorders Impaired fasting glucose subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2		
Vitamin D deficiency subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 October 2012	The following is a list of the major changes that were included in the amendment: • A secondary baseline from Week 1 from TKT028 could have been utilized for long-term safety and efficacy analyses. For this long-term analysis, the assumption was that there would be no delay in treatment between study TKT028 and HGT-REP-060. However, this second baseline analysis was not performed because 13 of the 35 enrolled subjects (37%) had a delay of at least 37 days between studies and, of these 13 subjects, 7 (20%) had a delay of at least 90 days. • Clarification was made that weight was to be recorded at the time points defined in the Schedule of Study Procedures, but that Replagal dose was to be calculated based on the subject's weight determined at Week 1 of HGT-REP-060. This dose was to remain fixed throughout the study. • Antibody testing for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) was permitted at the end of the TKT028 study (Week 52), after subject consent, allowing results to be received in time for HGT-REP-060 Week 1 confirmation of study entry criteria. • The window following possible or probable AEs was expanded to include the time until the event resolved or stabilized or an outcome was reached (whichever came first). • A definition of infusion related AEs was added as follows: - An infusion-related adverse event (IRAE) was defined as an AE that 1) occurred within 24 hours after the start of the infusion 2) began either during or after the infusion, and 3) was judged as possibly or probably related to study drug. Other AEs which occurred prior to the infusion, along with AEs associated with protocol-defined testing and assessments (eg, laboratory testing, electrocardiograms (ECGs), and physical examinations) which were performed prior to the infusion, were not defined as IRAEs. • The category of definitely related AEs was removed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported