Clinical trial results:
A Multicenter, Open-Label Study of Gene-Activated Human Glucocerebrosidase (GA-GCB) Enzyme Replacement Therapy in Patients with Type 1 Gaucher Disease Previously Treated with Imiglucerase

Summary

EudraCT number	2006-006304-11
Trial protocol	GB DE IT ES
Global end of trial date	26 June 2009

Results information

Result version number	v1 (current)
This version publication date	04 September 2018
First version publication date	21 January 2015

Trial information

Trial identification

Sponsor protocol code	TKT034

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00478647
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire Human Genetic Therapies, Inc.
Sponsor organisation address	300 Shire Way, Lexington, Massachusetts, United States, 02421
Public contact	Tiffany Crump, Shire Human Genetic Therapies, Inc., 044 484-595-8850, tcrump@shire.com
Scientific contact	Tiffany Crump, Shire Human Genetic Therapies, Inc., 044 484-595-8850, tcrump@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	26 June 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 June 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety of every other week dosing of velaglucerase alfa (GA-GCB) in subjects with type 1 Gaucher disease who were previously treated with imiglucerase.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki. It was also conducted in accordance with local country regulations and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) E6 guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 July 2007
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: 5
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Israel: 9
Country: Number of subjects enrolled	United States: 23
Worldwide total number of subjects	41
EEA total number of subjects	9

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)	2
Adolescents (12-17 years)	7
Adults (18-64 years)	28

From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first subject was enrolled on 25 July 2007 and the last subject completed on 26 June 2009. Subjects received the same dose of velaglucerase alfa (GA-GCB) as their previous dose of imiglucerase (range- </= 60 Unit per kilogram (U/kg) - >/=15 U/kg) every other week via intravenous infusion.

Pre-assignment

Screening details:

Subjects at least 2 years old with documented diagnosis of type 1 Gaucher disease. Consistent treatment (every other week at a dose <=/= 60 U/kg and >=/= 15 U/kg) with imiglucerase for at least 30 consecutive months; same dose during the 6 months prior to study enrollment. Minor dosing interval variance was allowed per standard clinical practice.

Period 1

Period 1 title	GA-GCB (Velaglucerase Alfa) (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	GA-GCB (Velaglucerase Alfa)

Arm description:

15-60 unit per kilogram (U/kg), every other week via intravenous infusion

Arm type	Experimental
Investigational medicinal product name	GA-GCB (velaglucerase alfa)
Investigational medicinal product code	
Other name	VPRIV®, GA-GCB, gene-activated® human glucocerebrosidase
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

15-60 U/kg, every other week via intravenous infusion

Number of subjects in period 1[1]	GA-GCB (Velaglucerase Alfa)
Started	40
Completed	38
Not completed	2
Consent withdrawn by subject	1
Adverse event	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: All enrolled (N=41) subjects were not treated with study drug. Since baseline period included only treated (N=40) subjects, the worldwide number enrolled in the trial differs with the number of subjects reported in the baseline period.

Baseline characteristics

Reporting groups	
Reporting group title	GA-GCB (Velaglucerase Alfa)
Reporting group description:	
15-60 U/kg, every other week via intravenous infusion	

Reporting group values	GA-GCB (Velaglucerase Alfa)	Total	
Number of subjects	40	40	
Age categorical Units: Subjects			
<=18 years	9	9	
Between 18 and 65 years	27	27	
>=65 years	4	4	
Age continuous Units: years			
arithmetic mean	35.6		
standard deviation	± 18.37	-	
Gender categorical Units: Subjects			
Female	22	22	
Male	18	18	
Baseline hemoglobin concentration Units: gram per deciliter (g/dL)			
median	13.775		
full range (min-max)	10.4 to 16.45	-	
Baseline liver volume Units: Percent (%) body weight			
median	1.9		
full range (min-max)	1.4 to 3.9	-	
Baseline spleen volume Units: Percent (%) body weight			
median	0.5		
full range (min-max)	0.2 to 3.2	-	
Baseline platelet count Units: 10^9 per litre (10^9/L)			
median	162		
full range (min-max)	29 to 399	-	

End points

End points reporting groups

Reporting group title	GA-GCB (Velaglucerase Alfa)
Reporting group description:	
15-60 unit per kilogram (U/kg), every other week via intravenous infusion	

Primary: Subjects Who Experienced at Least One Adverse Event

End point title	Subjects Who Experienced at Least One Adverse Event[1]
End point description:	
Safety was assessed throughout the study by assessments including adverse events, concomitant medication use, and vital signs. Additional safety assessments, including 12-lead ECGs, physical examinations, clinical laboratory tests and determination of the presence of anti-velaglucerase alfa antibodies. Safety population included subjects who have received at least 1 full or partial dose of study drug. Refer to Adverse event section for further details.	
End point type	Primary
End point timeframe:	
Week 53	

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 analyses for this end point

End point values	GA-GCB (Velaglucerase Alfa)			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: subjects				
Experienced at Least One Adverse Event	34			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 53 in Hemoglobin Concentration

End point title	Change From Baseline to Week 53 in Hemoglobin Concentration
End point description:	
Intent to Treat (ITT) population included subjects who have received at least 1 full or partial dose of study drug.	
End point type	Secondary
End point timeframe:	
Week 53	

End point values	GA-GCB (Velaglucerase Alfa)			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: g/dL				
arithmetic mean (confidence interval 90%)				
Hemoglobin Concentration	-0.101 (-0.272 to 0.07)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline to Week 53 in Platelet Count

End point title	Percent Change From Baseline to Week 53 in Platelet Count
End point description: ITT population.	
End point type	Secondary
End point timeframe: Week 53	

End point values	GA-GCB (Velaglucerase Alfa)			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percent (%) change				
arithmetic mean (confidence interval 90%)				
Platelet Count	7.04 (0.54 to 13.53)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline to Week 51 in Normalized Liver Volume

End point title	Percent Change From Baseline to Week 51 in Normalized Liver Volume

End point description:

Liver volume has been normalized for percentage (%) of body weight. Liver size relative to body

weight= (Liver volume [cc]/Body weight [kg])*100.

ITT Population.

End point type	Secondary

End point timeframe:

Week 51

End point values	GA-GCB (Velaglucerase Alfa)			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: Percent (%) change				
arithmetic mean (confidence interval 90%)				
Normalized Liver Volume	-0.03 (-2.62 to 2.56)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline to Week 51 in Normalized Spleen Volume

End point title	Percent Change From Baseline to Week 51 in Normalized Spleen Volume

End point description:

Spleen volume has been normalized for percentage (%) of body weight. Spleen size relative to body weight= (Spleen volume [cc]/Body weight [kg])*100.

ITT Population.

End point type	Secondary

End point timeframe:

Week 51

End point values	GA-GCB (Velaglucerase Alfa)			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: Percent (%) change				
arithmetic mean (confidence interval 90%)				
Normalized Spleen Volume	-5.56 (-10.77 to -0.35)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Time of informed consent until 30 days after the last dose and/or until the event was resolved/stabilized or outcome was reached, whichever came first. Subjects who discontinued/withdrew prior to Week 53, AEs were followed up to 30 days after last dose

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	9

Reporting groups

Reporting group title	GA-GCB (Velaglucerase Alfa)

Reporting group description:

15-60 U/kg, every other week via intravenous infusion

Serious adverse events	GA-GCB (Velaglucerase Alfa)		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 40 (10.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Immune system disorders			
Anaphylactoid reaction			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Drug hypersensitivity			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Swelling face			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urticaria			

subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 40 (2.50%)		
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	GA-GCB (Velaglucerase Alfa)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 40 (77.50%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	15		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	13		
Influenza like illness			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	5		
Malaise			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	33		
Non-Cardiac chest pain			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	3		
Pyrexia			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	7		
Respiratory, thoracic and mediastinal			

disorders Cough subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Pharyngolaryngeal pain subjects affected / exposed occurrences (all) Sinus congestion subjects affected / exposed occurrences (all)	 6 / 40 (15.00%) 6 3 / 40 (7.50%) 7 3 / 40 (7.50%) 6 6 / 40 (15.00%) 8 2 / 40 (5.00%) 2		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	 2 / 40 (5.00%) 2		
Investigations Activated partial thromboplastin time prolonged subjects affected / exposed occurrences (all) Blood glucose increased subjects affected / exposed occurrences (all)	 2 / 40 (5.00%) 2 3 / 40 (7.50%) 3		
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all) Procedural pain subjects affected / exposed occurrences (all)	 2 / 40 (5.00%) 2 2 / 40 (5.00%) 2		
Nervous system disorders			

Dizziness subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3		
Headache subjects affected / exposed occurrences (all)	12 / 40 (30.00%) 29		
Paraesthesia subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3		
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all)	5 / 40 (12.50%) 11		
Constipation subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Diarrhoea subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 4		
Nausea subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 4		
Toothache subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 3		
Vomiting subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Renal and urinary disorders			

Proteinuria subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) Rotator cuff syndrome subjects affected / exposed occurrences (all)	 8 / 40 (20.00%) 14 7 / 40 (17.50%) 10 2 / 40 (5.00%) 2 6 / 40 (15.00%) 7 5 / 40 (12.50%) 6 2 / 40 (5.00%) 3		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all) Rhinovirus infection	 3 / 40 (7.50%) 4 4 / 40 (10.00%) 4 8 / 40 (20.00%) 10 2 / 40 (5.00%) 2		

subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	7		
Urinary tract infection			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 October 2007	•Inclusion Criterion changed, requiring male subjects to use a medically acceptable method of birth control throughout their participation in the study and to report any pregnancy of a partner. •Exclusion Criterion was rewritten to clarify that exclusion required both a hemoglobin of less than equal to (<=) 10 g/dL and a platelet count of <=80 x 103 platelets/cubic millimetre(mm3). •Anaphylactoid reaction during treatment with imiglucerase in addition to anaphylactic reaction as a reason for exclusion from the study. •Expanded exclusion of erythropoietin to exclusion of any red cell growth factor and allowed the use of inhaled corticosteroid therapy. •Provided clarification that a spleen infarction was required to be active and clinically significant, experienced within 12 months of screening, and radiologically confirmed to be a reason for exclusion from the study and splenectomized subjects were not to be excluded. •Provided clarification that bone necrosis was to be worsening bone necrosis within 12 months of screening; inactive or stable bone necrosis was not intended to be an exclusion. •Pregnant or lactating subjects were excluded. •The following assessments were added to screening procedures: chitotriosidase genotyping, vital signs, and serum B12 and folic acid concentrations. •After each of the first 3 infusions, a safety telephone call from the Investigator to the subject 1 day after infusion was added to the protocol. •Infusion time was changed from the same infusion time as the previous imiglucerase dose to a 1-hour infusion. Longer infusion times were to be documented. •Transition to home therapy no longer required approval by the Shire HGT Medical Monitor but was left to the discretion and direction of the Investigator. •Reticulocyte count was to be performed at the site's local laboratory rather than a central laborator due to stability issues. •Imaging of the femoral neck was added to the dual-energy x-ray absorptiometry (DXA) assessment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported