



Clinical trial results:

A Multi-center, Open-label, Efficacy and Safety Study of Velaglucerase alfa Enzyme Replacement Therapy in Children and Adolescents with Type 3 Gaucher Disease

Summary

EudraCT number	2012-003427-38
Trial protocol	Outside EU/EEA
Global end of trial date	15 March 2015

Results information

Result version number	v1 (current)
This version publication date	01 December 2018
First version publication date	01 December 2018

Trial information

Trial identification

Sponsor protocol code	HGT-GCB-068
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01685216
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire
Sponsor organisation address	300 Shire Way, Lexington, United States, MA 02421
Public contact	Study Director, Shire, ClinicalTransparency@shire.com
Scientific contact	Study Director, Shire, ClinicalTransparency@shire.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 March 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial was to explore the efficacy and safety of velaglucerase alfa enzyme replacement therapy (ERT) in children and adolescents with type 3 Gaucher disease.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice (GCP) and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 September 2012
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	Egypt: 4
Country: Number of subjects enrolled	India: 1
Country: Number of subjects enrolled	Tunisia: 1
Worldwide total number of subjects	6
EEA total number of subjects	0

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)	5
Adolescents (12-17 years)	1
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0
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Subject disposition

Recruitment

Recruitment details:

The study was conducted at 6 centers in Egypt, India, and Tunisia between 14 Sep 2012 (first subject first visit) and 15 Mar 2015 (last subject last visit).

Pre-assignment

Screening details:

A total of 7 subjects were enrolled, of them 6 subjects received treatment.

Pre-assignment period milestones

Number of subjects started	6
Number of subjects completed	6

Period 1

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

Arms

Arm title	Velaglucerase alfa
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Arm description:

Subjects received an intravenous (IV) infusion of velaglucerase alfa at 60 U/kg, every other week for 1 year, then were followed for 1 month.

Arm type	Experimental
Investigational medicinal product name	Gene-Activated Human Glucocerebrosidase 400U/vial
Investigational medicinal product code	GA-GCB
Other name	VELAGLUCERASE ALFA
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received an intravenous (IV) infusion of velaglucerase alfa every other week for 1 year.

Number of subjects in period 1	Velaglucerase alfa
Started	6
Completed	6

Baseline characteristics

Reporting groups

Reporting group title	Velaglucerase alfa
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Reporting group description:

Subjects received an intravenous (IV) infusion of velaglucerase alfa at 60 U/kg, every other week for 1 year, then were followed for 1 month.

Reporting group values	Velaglucerase alfa	Total	
Number of subjects	6	6	
Age categorical			
Units: Subjects			
Age continuous			
The safety analysis population, included all subjects who received at least 1 study drug infusion (full or partial).			
Units: years			
arithmetic mean	5.17		
standard deviation	± 4.446	-	
Gender categorical			
The safety analysis population, included all subjects who received at least 1 study drug infusion (full or partial).			
Units: Subjects			
Female	1	1	
Male	5	5	

End points

End points reporting groups

Reporting group title	Velaglucerase alfa
Reporting group description:	
Subjects received an intravenous (IV) infusion of velaglucerase alfa at 60 U/kg, every other week for 1 year, then were followed for 1 month.	

Primary: Change From Baseline to 12 Months (Week 53) in Hemoglobin Concentration

End point title	Change From Baseline to 12 Months (Week 53) in Hemoglobin Concentration ^[1]
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End point description:

Hemoglobin concentration was measured as part of the hematology panel or measured separately when the hematology panel was not scheduled. Samples were measured by a central laboratory. Baseline is the modified baseline hemoglobin concentration, the average of the values from screening, baseline, and Week 1/Day 1. A positive change from baseline indicates that hemoglobin concentration increased. The intent-to-treat (ITT) population included all subjects who received at least 1 study drug infusion (full or partial). In the below table, the number of subjects analyzed signifies subjects who were evaluable for this measure

End point type	Primary
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End point timeframe:

Baseline, Week 53 or end of study

Notes:

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

Justification: Per protocol, only descriptive statistics were collected for this endpoint.

End point values	Velaglucerase alfa			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Grams per decilitre (g/dL)				
arithmetic mean (standard deviation)				
Hemoglobin	2.15 (± 1.213)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to 12 Months (Week 53) in Platelet Count

End point title	Change From Baseline to 12 Months (Week 53) in Platelet Count
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End point description:

Platelet count was measured at a central laboratory as part of the hematology panel. Baseline is the modified baseline platelet count, the average of the values from screening, baseline and Week 1/Day 1. A positive change from baseline indicates that platelet count increased. The ITT population included all subjects who received at least 1 study drug infusion (full or partial). In the below table, the number of subjects analyzed signifies subjects who were evaluable for this measure.

End point type	Secondary
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End point timeframe:

Baseline, Week 53

End point values	Velaglucerase alfa			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: (10 ⁹)/L				
arithmetic mean (standard deviation)				
Platelets	136.6 (± 51.48)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline to 12 Months (Week 51) in Normalized Liver Volume Measured Using Magnetic Resonance Imaging (MRI)

End point title	Percent Change From Baseline to 12 Months (Week 51) in Normalized Liver Volume Measured Using Magnetic Resonance Imaging (MRI)
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End point description:

Quantitative abdominal MRI was used to measure liver volume. If sedation was necessary to perform an MRI and the investigator deemed that this would be an unwarranted risk to the subject, liver volume could have been measured by ultrasound. Organ volume was measured by a single independent reviewer who was blinded to the subject identification and time point. The liver size relative to body weight was determined using the corresponding body weight measured at the same visit. Change in liver volume is presented as the normalized percentage of body weight. A negative change from baseline indicates that liver volume decreased. The ITT population included all subjects who received at least 1 study drug infusion (full or partial). In the below table, the number of subjects analyzed signifies subjects who were evaluable for this measure.

End point type	Secondary
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End point timeframe:

Baseline, Week 51 or end of study

End point values	Velaglucerase alfa			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Percent change				
arithmetic mean (standard deviation)				
Normalized Liver Volume	-30.12 (± 10.366)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline to 12 Months (Week 51) in Normalized Spleen Volume Measured Using Magnetic Resonance Imaging (MRI)

End point title	Percent Change From Baseline to 12 Months (Week 51) in Normalized Spleen Volume Measured Using Magnetic Resonance Imaging (MRI)
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End point description:

Quantitative abdominal MRI was used to measure spleen volume. If sedation was necessary to perform an MRI and the investigator deemed that this would be an unwarranted risk to the subject, spleen volume could have been measured by ultrasound. Organ volume was measured by a single independent reviewer who was blinded to the subject identification and time point. The spleen size relative to body weight was determined using the corresponding body weight measured at the same visit. Change in spleen volume is presented as the normalized percentage of body weight. A negative change from baseline indicates that spleen volume decreased. The ITT population included all subjects who received at least 1 study drug infusion (full or partial). In the below table, the number of subjects analyzed signifies subjects who were evaluable for this measure.

End point type	Secondary
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End point timeframe:

Baseline, Week 51

End point values	Velaglucerase alfa			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Percent change				
arithmetic mean (standard deviation)				
Normalized Spleen Volume	-62.27 ($\pm$ 19.991)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Abnormal Neurological Status During the Study

End point title	Number of Subjects With Abnormal Neurological Status During the Study
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End point description:

Neurological symptoms were evaluated at regular intervals during the study and assessed on an individualized basis by a limited, age- and developmental stage-appropriate neurological examination adapted to suit the status of each subject. It was preferred that each neurological examination be performed by a neurologist with experience in assessment of neurological symptoms in patients with Gaucher disease and, if possible, the same neurologist (or designee) who evaluated a given subject at baseline performed the neurological examinations scheduled for that subject during the treatment phase and at the end of study visit. The ITT population included all subjects who received at least 1 study drug infusion (full or partial).

End point type	Secondary
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End point timeframe:

Baseline, Weeks 13, 25, 37, and 53 or end of study

End point values	Velaglucerase alfa			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Subjects				
Subjects With Abnormal Neurological Status	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects who Experienced a Treatment-Emergent Adverse Event

End point title	Number of Subjects who Experienced a Treatment-Emergent Adverse Event
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End point description:

Adverse events (AEs) were monitored continuously throughout the study from the time the subject or subjects parent/legal guardian signed the informed consent/assent (if applicable) until 30 days after the subject's last dose of study drug or at the end of study visit and/or until the event resolved or stabilized, or an outcome had been reached, whichever came first. Treatment-emergent adverse events (TEAEs) were defined as AEs which occurred on or after the time of the first infusion until 30 days after the subject's last study infusion. An infusion-related reaction is defined as an AE that 1) began either during or within 12 hours after the start of the infusion, and 2) was judged as possibly or probably related to study medication. The safety analysis population, included all subjects who received at least 1 study drug infusion (full or partial).

End point type	Secondary
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End point timeframe:

From start of study drug administration to follow-up (up to 57 weeks)

End point values	Velaglucerase alfa			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Subjects				
Any TEAE	6			
Serious TEAE	1			
Infusion-related Reaction	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subject who Developed Anti-Velaglucerase Alfa Antibodies

During the Study

End point title	Number of Subject who Developed Anti-Velaglycerase Alfa Antibodies During the Study
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End point description:

Subjects provided blood samples for measurement of anti-velaglycerase alfa antibodies in serum at baseline and approximately every 12 weeks during the treatment phase. Blood samples collected during the treatment phase were to be drawn prior to infusions. Analysis of anti-velaglycerase antibodies used a validated 3-tier immunoassay method (screening, confirmatory, and titer). The ITT population included all subjects who received at least 1 study drug infusion (full or partial).

End point type	Secondary
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End point timeframe:

Baseline, Weeks 13, 25, 37 and 53

End point values	Velaglycerase alfa			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Subjects				
Baseline	0			
Week 13	1			
Week 25	1			
Week 37	1			
Week 53	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study drug administration to follow-up (up to 57 weeks)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.0
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Reporting groups

Reporting group title	Velaglucerase alfa
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Reporting group description:

Subjects received an intravenous (IV) infusion of velaglucerase alfa at 60 U/kg, every other week for 1 year, then were followed for 1 month.

Serious adverse events	Velaglucerase alfa		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	1 / 6 (16.67%)		
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	Velaglucerase alfa		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)		
Injury, poisoning and procedural complications			
Excoriation			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Fall			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		

Chilblains			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Procedural pain			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	8		
Convulsion			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Fine motor delay			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Gross motor delay			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Muscle spasticity			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		
Anaemia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Iron deficiency anaemia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Neutropenia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Thrombocytopenia			

subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 6 (66.67%)		
occurrences (all)	17		
Gait disturbance			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Influenza like illness			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Asthenia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Strabismus			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	5		
Gingival bleeding			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Inguinal hernia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Vomiting			

subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	3		
Asthma			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Productive cough			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Rhinorrhoea			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Wheezing			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Heat rash			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Rash papular			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	6		
Bone pain			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	6		
Myalgia			

subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Musculoskeletal pain			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Synovial cyst			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	4		
Acute tonsillitis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Hordeolum			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Oral herpes			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Postprocedural cellulitis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		

Rhinitis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 December 2010	- The patients were to have anemia at screening and at least 1 of 3 additional criteria (at least moderate splenomegaly, thrombocytopenia, or a readily palpable enlarged liver). - Change in the liver and spleen endpoints to indicate that the organ volumes would be determined by magnetic resonance imaging (MRI), not ultrasound, unless sedation would be required to perform the MRI and the investigator deemed that this would pose an unwarranted risk to the patient. - Change in immunoassay methods for evaluation of anti-velaglucerase alfa antibodies: Serum samples will be collected for evaluation of anti-velaglucerase alfa antibodies. Analysis of anti-velaglucerase alfa antibodies will be conducted using validated 3-tier immunoassay methods (screening, confirmatory, and titer) and the anti-velaglucerase alfa antibody positive samples will be further tested for the presence of neutralizing antibodies (NAb).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported