



## Clinical trial results:

### An Open-label, Multicenter, Single-arm, Phase 4 Study of the Effect of Treatment with Velaglucerase alfa on Bone-related Pathology in Treatment-naïve Patients with Type 1 Gaucher Disease

#### Summary

EudraCT number	2015-001578-17
Trial protocol	GB DE ES IT
Global end of trial date	30 November 2020

#### Results information

Result version number	v1 (current)
This version publication date	15 December 2021
First version publication date	15 December 2021

#### Trial information

##### Trial identification

Sponsor protocol code	SHP-GCB-402
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02574286
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, ClinicalTransparenc@takeda.com
Scientific contact	Study Director, Shire, ClinicalTransparenc@takeda.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	30 November 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	30 November 2020
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The main objective of the study is to evaluate the effect of velaglucerase alfa (VPRIV) therapy (60 units per kilogram [U/kg] every other week [EOW]) in treatment-naïve subjects with type 1 Gaucher disease on change from baseline in lumbar spine (LS) bone mineral density (BMD) Z-score as measured by dual energy x-ray absorptiometry (DXA) after 24 months of treatment.

Protection of trial subjects:

The study was conducted in accordance with current applicable industry regulations, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guideline E6 (1996) and any updates, European Union (EU) Directive 2001/20/EC and its updates, the ethical principles in the Declaration of Helsinki, and local ethical and legal requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 June 2016
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	United States: 4
Country: Number of subjects enrolled	Israel: 12
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United Kingdom: 3
Worldwide total number of subjects	21
EEA total number of subjects	2

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)	19
From 65 to 84 years	2
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

This study was conducted in the United States, Israel, Spain and United Kingdom from 07 June 2016 (first subjects first visit) to 30 November 2020 (last subjects last visit)

### Pre-assignment

Screening details:

A total of 21 subjects were enrolled and received treatment in this study.

### Period 1

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

### Arms

<b>Arm title</b>	Velaglucerase alfa 60 U/kg
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Arm description:

Subjects received 60-minute intravenous (IV) infusion of 60 U/kg velaglucerase alfa EOW for 24 months (up to 101 weeks).

Arm type	Experimental
Investigational medicinal product name	Velaglucerase alfa
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received 60-minute IV infusion of 60 U/kg velaglucerase alfa EOW for 24 months.

Number of subjects in period 1	Velaglucerase alfa 60 U/kg
Started	21
Completed	16
Not completed	5
Adverse event, non-fatal	3
Withdrawal by Subject	2

## Baseline characteristics

### Reporting groups

Reporting group title	Velaglucerase alfa 60 U/kg
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Reporting group description:

Subjects received 60-minute intravenous (IV) infusion of 60 U/kg velaglucerase alfa EOW for 24 months (up to 101 weeks).

Reporting group values	Velaglucerase alfa 60 U/kg	Total	
Number of subjects	21	21	
Age Categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	43.9 ± 14.2	-	
Gender categorical Units: Subjects			
Female	11	11	
Male	10	10	
Race Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	20	20	
More than one race	1	1	
Unknown or Not Reported	0	0	
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	19	19	
Unknown or Not Reported	2	2	

## End points

### End points reporting groups

Reporting group title	Velaglugerace alfa 60 U/kg
Reporting group description:	
Subjects received 60-minute intravenous (IV) infusion of 60 U/kg velaglugerace alfa EOW for 24 months (up to 101 weeks).	

### Primary: Change From Baseline in Lumbar Spine (LS) Bone Mineral Density (BMD) Z-Score up to End of Study (EOS) (Week 103)

End point title	Change From Baseline in Lumbar Spine (LS) Bone Mineral Density (BMD) Z-Score up to End of Study (EOS) (Week 103) <sup>[1]</sup>
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#### End point description:

BMD of the LS was measured by dual energy x-ray absorptiometry (DXA), and the result was converted to Z-scores appropriate for age, sex, and race. The Z-score indicated the number of standard deviations away from a reference population in the same age range, race and with the same sex. A Z-score of 0 was equal to the mean. Negative numbers indicated values lower than the mean and positive numbers indicated values higher than the mean. Baseline was defined as last data collected prior to the first administration of study drug. Change from baseline in lumbar spine BMD Z-Score up to EOS (Week 103) was reported. Intent-to-Treat (ITT) Population was defined as all enrolled subjects who received at least one study drug infusion (full or partial). Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint.

End point type	Primary
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#### End point timeframe:

Baseline up to EOS (Week 103)

#### 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: Only descriptive data was planned to be analyzed for this endpoint.

<b>End point values</b>	Velaglugerace alfa 60 U/kg			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Z-score				
arithmetic mean (standard deviation)	0.17 (± 0.394)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Lumbar Spine (LS) BMD Z-score at Week 51

End point title	Change From Baseline in Lumbar Spine (LS) BMD Z-score at Week 51
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#### End point description:

BMD of the LS was measured by DXA, and the results was converted to Z-scores appropriate for age, sex, and race. The Z-score indicated the number of standard deviations away from a reference population in the same age range, race and with the same sex. A Z-score of 0 was equal to the mean. Negative numbers indicated values lower than the mean and positive numbers indicated values higher than the mean. Baseline was defined as last data collected prior to the first administration of study drug. Change From baseline in LS BMD Z-score at Week 51 was reported. ITT Population was defined as all

enrolled subjects who received at least one study drug infusion (full or partial). Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Baseline, Week 51

<b>End point values</b>	Velaglucerase alfa 60 U/kg			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Z-Score				
arithmetic mean (standard deviation)	0.02 (± 0.431)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Lumbar Spine BMD at Week 51 and EOS (Week 103)

End point title	Change From Baseline in Lumbar Spine BMD at Week 51 and EOS (Week 103)
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End point description:

BMD of the LS was measured by dual energy x-ray absorptiometry (DXA), and the results was measured in gram per square centimeter (g/cm<sup>2</sup>). Baseline was defined as last data collected prior to the first administration of study drug. Change From baseline in LS BMD at Week 51 and EOS (Week 103) was reported. ITT Population was defined as all enrolled subjects who received at least one study drug infusion (full or partial). Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Baseline, Week 51 and EOS (Week 103)

<b>End point values</b>	Velaglucerase alfa 60 U/kg			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: g/cm <sup>2</sup>				
arithmetic mean (standard deviation)				
Change at Week 51	0.006 (± 0.0342)			
Change at EOS (Week 103)	0.011 (± 0.0474)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Bone Marrow Burden (BMB) Score at Week 51 and EOS (Week 103)

End point title	Change From Baseline in Bone Marrow Burden (BMB) Score at Week 51 and EOS (Week 103)
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End point description:

BMB score was a semi-quantitative magnetic resonance imaging (MRI) scoring system for assessing the extent of bone marrow involvement in Gaucher disease. BMB scores was calculated from MRI of the LS and femurs with a range from 0 (no abnormalities) to 8 points (severe disease). A positive BMB score indicated more severe bone marrow involvement and negative BMB score indicated less severe bone marrow involvement. Baseline was defined as last data collected prior to the first administration of study drug. ITT Population was defined as all enrolled subjects who received at least one study drug infusion (full or partial). Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint and "number analysed" signifies subjects who were evaluable at specific time point.

End point type	Secondary
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End point timeframe:

Baseline, Week 51 and EOS (Week 103)

<b>End point values</b>	Velaglucerase alfa 60 U/kg			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Score on a Scale				
arithmetic mean (standard deviation)				
Change at Week 51(n=15)	-3.0 (± 1.85)			
Change at EOS (Week 103) (n=13)	-3.0 (± 2.27)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Hemoglobin Concentration at Week 13, 25, 37, 51, 65, 77, 89, and EOS (Week 103)

End point title	Change From Baseline in Hemoglobin Concentration at Week 13, 25, 37, 51, 65, 77, 89, and EOS (Week 103)
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End point description:

Blood samples were collected for measurement of hemoglobin concentration. Baseline was defined as last data collected prior to the first administration of study drug. Change from baseline in hemoglobin concentration at Week 13, 25, 37, 51, 65, 77, 89, and EOS (Week 103) was reported. ITT Population was defined as all enrolled subjects who received at least one study drug infusion (full or partial). Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint and "number analysed" signifies subjects who were evaluable at specific time point.

End point type	Secondary
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End point timeframe:

Baseline, Week 13, 25, 37, 51, 65, 77, 89, and EOS (Week 103)



<b>End point values</b>	Velaglucerase alfa 60 U/kg			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: grams per deciliter (g/dL)				
arithmetic mean (standard deviation)				
Change at Week 13 (n=17)	0.532 (± 0.7624)			
Change at Week 25 (n=18)	0.764 (± 0.6688)			
Change at Week 37 (n=17)	0.765 (± 0.7836)			
Change at Week 51 (n=17)	0.935 (± 0.6588)			
Change at Week 65 (n=17)	1.029 (± 0.8239)			
Change at Week 77 (n=13)	1.015 (± 1.1577)			
Change at Week 89 (n=13)	1.138 (± 0.8910)			
Change at Week EOS (Week 103) (n=18)	0.897 (± 1.2309)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Platelet Count at Week 13, 25, 37, 51, 65, 77, 89, and EOS (Week 103)

End point title	Change From Baseline in Platelet Count at Week 13, 25, 37, 51, 65, 77, 89, and EOS (Week 103)
End point description:	
Blood samples were collected for measurement of platelet count. Baseline was defined as last data collected prior to the first administration of study drug. Change from baseline over time in platelet count at Week 13, 25, 37, 51, 65, 77, 89, and EOS (Week 103) was reported. ITT Population was defined as all enrolled subjects who received at least one study drug infusion (full or partial). Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint and "number analysed" signifies subjects who were evaluable at specific time point.	
End point type	Secondary
End point timeframe:	
Baseline, Week 13, 25, 37, 51, 65, 77, 89, and EOS (Week 103)	

<b>End point values</b>	Velaglucerase alfa 60 U/kg			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: 10 <sup>9</sup> platelets per liter				
arithmetic mean (standard deviation)				
Change at Week 13 (n=16)	38.06 (± 35.571)			
Change at Week 25 (n=17)	53.24 (± 46.955)			

Change at Week 37 (n=15)	62.23 (± 46.834)			
Change at Week 51 (n=16)	79.66 (± 89.701)			
Change at Week 65 (n=16)	75.03 (± 52.163)			
Change at Week 77 (n=13)	87.19 (± 70.528)			
Change at Week 89 (n=12)	71.96 (± 60.772)			
Change at Week EOS (Week 103) (n=16)	69.16 (± 53.451)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Normalized Liver Volume at Week 51 and EOS (Week 103)

End point title	Change From Baseline in Normalized Liver Volume at Week 51 and EOS (Week 103)
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End point description:

Normalized liver volume was measured by abdominal MRI. Baseline was defined as last data collected prior to the first administration of study drug. Liver volume has been normalized for percent (%) body weight. Liver size relative to body weight = (Liver volume [cubic centimeter (cc)]/Body weight [kg])\*100. Change from baseline in normalized liver volume at Week 51 and EOS (Week 103) was reported. ITT Population was defined as all enrolled subjects who received at least one study drug infusion (full or partial). Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint and "number analysed" signifies subjects who were evaluable at specific time point.

End point type	Secondary
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End point timeframe:

Baseline, Week 51 and EOS (Week 103)

End point values	Velaglucerase alfa 60 U/kg			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: percent body weight				
arithmetic mean (standard deviation)				
Change at Week 51 (n=17)	-0.353 (± 0.3485)			
Change at Week EOS (Week 103) (n=15)	-0.447 (± 0.4048)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Normalized Spleen Volume at Week 51 and EOS

**(Week 103)**

End point title	Change From Baseline in Normalized Spleen Volume at Week 51 and EOS (Week 103)
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## End point description:

Normalized spleen volume was measured by MRI. Spleen volume was normalized for % of body weight. Spleen size relative to body weight= (Spleen volume [cc]/Body weight [kg])\*100. Baseline was defined as last data collected prior to the first administration of study drug. Change from baseline in normalized spleen volume at Week 51 and EOS (Week 103) was reported. ITT Population was defined as all enrolled subjects who received at least one study drug infusion (full or partial). Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint and "number analysed" signifies subjects who were evaluable at specific time point.

End point type	Secondary
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## End point timeframe:

Baseline, Week 51 and EOS (Week 103)

<b>End point values</b>	Velaglucerase alfa 60 U/kg			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: percent body weight				
arithmetic mean (standard deviation)				
Change at Week 51 (n=17)	-0.443 (± 0.5987)			
Change at Week EOS (Week 103) (n=15)	-0.556 (± 0.7398)			

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Change From Baseline in Severity of Bone Pain at Week 51 and EOS (Week 103)**

End point title	Change From Baseline in Severity of Bone Pain at Week 51 and EOS (Week 103)
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## End point description:

Bone pain was measured by questions taken from the Brief Pain Inventory-short form (BPI-SF). Pain severity was evaluated based on the average of 4 questions from BPI-SF (Questions 3 to 6) assessing worst pain, least pain, average pain, pain right now, each rated on a scale from 0 (no pain) to 10 (pain as bad as you can imagine) with mild pain-score (0 to 4), moderate pain-score (5 to 6), and severe pain-score (7 to 10). Overall severity score was calculated as average of 4 questions ranging from 0 (no pain) to 10 (pain as bad as you can imagine). A negative change from baseline score indicates improvement. Baseline was defined as last data collected prior to the first administration of study drug. ITT Population was defined as all enrolled subjects who received at least one study drug infusion (full or partial). Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint and "99999" signifies standard deviation was not estimated due to single subject.

End point type	Secondary
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## End point timeframe:

Baseline, Week 51 and EOS (Week 103)

<b>End point values</b>	Velaglucerase alfa 60 U/kg			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Score on a Scale				
arithmetic mean (standard deviation)				
Change at Week 51	-2.750 (± 99999)			
Change at EOS (Week 103)	-3.250 (± 99999)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Bone Pain Interference Score at Weeks 51 and EOS (Week 103)

End point title	Change From Baseline in Bone Pain Interference Score at Weeks 51 and EOS (Week 103)
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End point description:

Bone pain interference was measured by questions taken from the BPI-SF. Pain interference was evaluated based upon average of 7 questions from BPI-SF (9A through 9G) regarding the extent to which pain interfered with daily activities, including general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life in the last 24 hours, each rated on a scale from 0 (does not interfere) to 10 (completely interferes). Overall pain interference score was calculated as average of 7 questions ranging from 0 (does not interfere) to 10 (completely interferes). A negative change from baseline score indicates improvement. Baseline was defined as last data collected prior to the first administration of study drug. ITT analysis population set. Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint and "99999" signifies standard deviation was not estimated due to single subject.

End point type	Secondary
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End point timeframe:

Baseline, Week 51 and EOS (Week 103)

<b>End point values</b>	Velaglucerase alfa 60 U/kg			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Score on a Scale				
arithmetic mean (standard deviation)				
Change at Week 51	-1.286 (± 99999)			
Change at Week EOS (Week 103)	-4.429 (± 99999)			

## Statistical analyses

No statistical analyses for this end point

**Secondary: Change From Baseline in Overall Fatigue Measured by Brief Fatigue Inventory (BFI) at Week 51 and EOS (Week 103)**

End point title	Change From Baseline in Overall Fatigue Measured by Brief Fatigue Inventory (BFI) at Week 51 and EOS (Week 103)
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## End point description:

Overall fatigue was measured by the BFI. BFI was a 9-item questionnaire developed to assess subjective fatigue. Each question asked the respondent to rate the level of their experienced fatigue over the past 24 hours on an 11- point (0-10) scale. First 3 questions-fatigue severity at current, usual, and worst levels, with 0="no fatigue" and 10="fatigue". Next 6 questions-level fatigue interference with daily activities included general activity, mood, walking ability, normal work (both inside and outside the home), relations with other people, and enjoyment of life. A score ranged from 0="no interference" and 10="complete interference. Overall fatigue score was calculated as average score of all 9 items on the BFI ranging from 0="no fatigue" to 10="as bad as you can imagine". Negative numbers=values lower than mean; positive numbers=values higher than mean. ITT Population. "Number of subjects analysed" signifies subjects who were evaluable for this endpoint.

End point type	Secondary
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## End point timeframe:

Baseline, Week 51 and EOS (Week 103)

<b>End point values</b>	Velaglucerase alfa 60 U/kg			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Score on a Scale				
arithmetic mean (standard deviation)				
Change at Week 51	-0.111 ( $\pm$ 1.4551)			
Change at EOS (Week 103)	0.044 ( $\pm$ 3.7132)			

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Number of Subjects With Shift in World Health Organization (WHO) BMD Classifications Based on LS T-Scores at Week 51 and EOS (Week 103)**

End point title	Number of Subjects With Shift in World Health Organization (WHO) BMD Classifications Based on LS T-Scores at Week 51 and EOS (Week 103)
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## End point description:

WHO BMD Classifications (Normal Bone Density, Osteopenia, Osteoporosis), bone mineral density was classified based on LS BMD T-scores. BMD T-score was a comparison of an individual's BMD compared to "normal". Also, BMD T-score is the standard deviation of the difference between measured BMD and that of the healthy young adult "normal". The T-score scale was as follows: -1 and above=normal, -1 to -2.5 = osteopenia (below normal and may lead to osteoporosis), and -2.5 and below=osteoporosis. Number of subjects with shift in WHO BMD classifications based on LS T-Scores at Week 51 and EOS (Week 103) were reported. ITT Population was defined as all enrolled subjects who received at least one study drug infusion (full or partial). Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint and "number analysed" signifies subjects who were evaluable at specific time point.

End point type	Secondary
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## End point timeframe:

Baseline, Week 51 and EOS (Week 103)

End point values	Velaglucerase alfa 60 U/kg			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Subjects				
Normal Baseline- Normal Week 51 (n=0)	0			
Normal Baseline- Osteopenia Week 51 (n=0)	0			
Normal Baseline- Osteoporosis Week 51 (n=0)	0			
Osteopenia Baseline- Normal Week 51 (n=10)	1			
Osteopenia Baseline- Osteopenia Week 51 (n=10)	6			
Osteopenia Baseline- Osteoporosis Week 51 (n=10)	3			
Osteoporosis Baseline- Normal Week 51(n=6)	0			
Osteoporosis Baseline- Osteopenia Week 51 (n=6)	0			
Osteoporosis Baseline- Osteoporosis Week 51 (n=6)	6			
Normal Baseline- Normal Week 103 (n=1)	1			
Normal Baseline- Osteopenia Week 103 (n=1)	0			
Normal Baseline- Osteoporosis Week 103 (n=1)	0			
Osteopenia Baseline- Normal Week 103 (n=10)	2			
Osteopenia Baseline- Osteopenia Week 103 (n=10)	6			
Osteopenia Baseline- Osteoporosis Week 103 (n=10)	2			
Osteoporosis Baseline- Normal Week 103 (n=5)	0			
Osteoporosis Baseline- Osteopenia Week 103 (n=5)	0			
Osteoporosis Baseline- Osteoporosis Week 103 (n=5)	5			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs)
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End point description:

An adverse event (AE) was any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. A TEAE was defined as any AE that occurred on or after the time of the first infusion of study

drug until 30 days after the last infusion of study drug. Number of subjects with TEAEs were reported. Safety population was defined as all enrolled subjects who received at least one study drug infusion (full or partial).

End point type	Secondary
End point timeframe:	
From start of study drug infusion up to follow-up (107 weeks)	

<b>End point values</b>	Velaglucerase alfa 60 U/kg			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: Subjects	21			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects Who Developed Positive Antivelaglucerase Alfa Antibody Status

End point title	Number of Subjects Who Developed Positive Antivelaglucerase Alfa Antibody Status
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End point description:

Anti-velaglucerase alfa antibody included antivelaglucerase antibodies (ADA) and neutralizing antivelaglucerase antibodies (NAb). The Anti-velaglucerase antibody status was summarized as categorical variable by positive and negative. Number of subjects who developed positive anti-velaglucerase alfa antibody were reported. Safety population was defined as all enrolled subjects who received at least one study drug infusion (full or partial).

End point type	Secondary
End point timeframe:	
Baseline up to EOS (Week 103)	

<b>End point values</b>	Velaglucerase alfa 60 U/kg			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: Subjects	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 infusion up to follow-up (107 weeks)

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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### Reporting groups

Reporting group title	Velaglucerase alfa 60 U/kg
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Reporting group description:

Subjects received 60-minute intravenous (IV) infusion of 60 units per kilogram (U/kg) velaglucerase alfa every other Week (EOW) for 24 months (up to 101 weeks).

Serious adverse events	Velaglucerase alfa 60 U/kg		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 21 (9.52%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pyelonephritis			
subjects affected / exposed	1 / 21 (4.76%)		
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 60 U/kg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 21 (95.24%)		
General disorders and administration site conditions			



Influenza like illness subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2		
Asthenia subjects affected / exposed occurrences (all)	3 / 21 (14.29%) 3		
Fatigue subjects affected / exposed occurrences (all)	5 / 21 (23.81%) 6		
Non-cardiac chest pain subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2		
Injection site bruising subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2		
Pain subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2		
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)	6 / 21 (28.57%) 11		
Rhinorrhoea subjects affected / exposed occurrences (all)	3 / 21 (14.29%) 3		
Cough subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 3		
Nasal congestion subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2		
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2		
Investigations			

Blood iron decreased subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2		
C-reactive protein increased subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2		
Injury, poisoning and procedural complications Infusion related reaction subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 4		
Cardiac disorders Bundle branch block right subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2		
Nervous system disorders Headache subjects affected / exposed occurrences (all)  Dizziness subjects affected / exposed occurrences (all)	6 / 21 (28.57%) 15  5 / 21 (23.81%) 11		
Eye disorders Eye pain subjects affected / exposed occurrences (all)	3 / 21 (14.29%) 3		
Gastrointestinal disorders Gastroesophageal reflux disease subjects affected / exposed occurrences (all)  Nausea subjects affected / exposed occurrences (all)  Constipation subjects affected / exposed occurrences (all)  Dyspepsia	3 / 21 (14.29%) 4  3 / 21 (14.29%) 4  2 / 21 (9.52%) 2		

subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 4		
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Urticaria			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	11 / 21 (52.38%)		
occurrences (all)	20		
Pain in extremity			
subjects affected / exposed	8 / 21 (38.10%)		
occurrences (all)	15		
Arthralgia			
subjects affected / exposed	5 / 21 (23.81%)		
occurrences (all)	6		
Myalgia			
subjects affected / exposed	4 / 21 (19.05%)		
occurrences (all)	5		
Musculoskeletal pain			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	3		
Bone pain			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Joint swelling			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Muscle spasms			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	4		
Infections and infestations			

Pneumonia subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2		
Nasopharyngitis subjects affected / exposed occurrences (all)	5 / 21 (23.81%) 6		
Urinary tract infection subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 3		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2		
Metabolism and nutrition disorders Vitamin D deficiency subjects affected / exposed occurrences (all)	4 / 21 (19.05%) 4		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 September 2015	Protocol Amendment 1: -Added details about emergency contact information. -Updated the details in exploratory objectives endpoints. -Added new section about home infusion of VPRIV. -Updated safety language to bring it into alignment with Shire standard language.
02 June 2016	Protocol Amendment 2: -Added information that all subjects will receive "600 IU 25 hydroxyvitamin D (oral) daily" as concomitant medication. -Changed the evaluation of primary endpoint from 12 months to 24 months. -Changed the evaluation of secondary endpoint from 24 months to 12 months. -Timepoints for measurements of hemoglobin concentration and platelet count were changed to baseline and weeks 13, 25, 37, 51, 65, 77, 89, and 103 (end of study). -Clarified biomarkers for analysis. -Revised age range to $\geq 18$ and $\leq 65$ years of age. -Updated emergency contact information. -Added specific guidance for contraception.
06 July 2016	Protocol Amendment 3: -The minimum age for inclusion had been changed to 18 years; therefore, informed consent by parents was eliminated. -Added "HBsAg, HCV, HIV, and 25 hydroxyvitamin D blood test" as a safety laboratory tests to be performed at screening. -Changed the assessment of primary efficacy endpoint at the baseline visit to occur at the screening visit instead.
04 May 2017	Protocol Amendment 4: -The dose of Vitamin D was revised from 600 IU to 800 IU. -The subject age range for the enrollment in the study was increased from $\geq 18$ and $\leq 65$ to $\geq 18$ and $\leq 70$ years. -The definition of IRR was updated to match the definition in summary of product characteristics. -The assessments of BMB and LS BMD Z score were eliminated at Week 25 and Week 77 to ease subject burden as data from these visits will not be used in the determination of any endpoints. -Added criterion of BMD T-score to facilitate enrollment after consideration of this measure as an appropriate alternative to BMD Z-score. -Deleted "Change in the quadriceps cross sectional area and measures of relevance to determine lean muscle mass are additional exploratory endpoints." as the proper imaging modality for its measurement was not being performed and MRI was no longer considered to be an adequate measure. -The window of study procedures was changed to $\pm 7$ days to allow for subject rescheduling and to facilitate protocol execution.--
26 July 2018	Protocol Amendment 5: -The number of subjects planned for enrollment was reduced from approximately 40 subjects to at least 19 subjects. -The number of expected evaluable subjects was decreased from 34 subjects to 13 subjects. -The key secondary objectives were re-classified as secondary objectives. -The BMB scoring was changed to follow the DeMayo et al. method instead of the Maas et al. method. -The power provided by the sample size for the detection of change in the primary endpoint was changed from 99% to 90%. -The early subject discontinuation rate previously estimated at 15% was revised to 30%. -Viral testing was removed from the list of screening visit assessments.

02 October 2020	<p>Protocol Amendment 6:</p> <ul style="list-style-type: none"> <li>- Two new objectives and endpoints were added.</li> </ul> <p>Objective:</p> <ul style="list-style-type: none"> <li>* BMD as measured by the change from baseline in g/cm2 after 12 months of treatment.</li> <li>* BMD as measured by the change from baseline in g/cm2 after 24 months of treatment.</li> </ul> <p>Endpoints:</p> <ul style="list-style-type: none"> <li>* Change from baseline to 12 months (Week 51) in BMD reported as g/cm2. Assessments will be performed at the screening visit and Weeks 51.</li> <li>* Change from baseline to 24 months (Week 103 [end of study]) in BMD reported as g/cm2. Assessments will be performed at the screening visit and Week 103 (end of study)</li> <li>- The Brief Pain Inventory – Short Form was updated to “Questions taken from the BPI-SF©”</li> <li>- Added the optional transfer of study visit weeks 77 and/or 89 to home therapy and the addition of dose continuation infusions due to the COVID-19 pandemic.</li> <li>- Added that infusion of VPRIV may be delivered intravenously with an in-line sterilizing filter that has a rated pore size of 0.22 micrometer (mcm).</li> </ul>
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Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported