Clinical trial results:
A Multicenter, Randomized, Placebo-controlled Study of SBC-102 in Patients with Lysosomal Acid Lipase Deficiency (ARISE [Acid Lipase Replacement Investigating Safety and Efficacy])

Summary

EudraCT number	2011-002750-31
Trial protocol	DE GB IT ES CZ PL GR HR FR
Global end of trial date	12 December 2018

Results information

Result version number	v3
This version publication date	23 June 2019
First version publication date	06 August 2015
Version creation reason	• New data added to full data set Updated to include data from the Open-label Period of the study.

Trial information

Trial identification

Sponsor protocol code	LAL-CL02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01757184
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alexion Pharmaceuticals Inc.
Sponsor organisation address	121 Seaport Blvd, Boston, MA, United States, 02210
Public contact	European Clinical Trial Information, Alexion Pharmaceuticals Inc., +33 147100606, clinicaltrials.eu@alexion.com
Scientific contact	European Clinical Trial Information, Alexion Pharmaceuticals Inc., +33 147100606, clinicaltrials.eu@alexion.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001331-PIP01-12
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	12 December 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to demonstrate efficacy of sebelipase alfa relative to placebo, based on normalisation of alanine aminotransferase (ALT) in participants with lysosomal acid lipase deficiency.

Protection of trial subjects:

Participants have the right to withdraw from the study at any time for any reason without prejudice to further treatment. The investigator and Sponsor also have the right to withdraw participants from the study at any time. Specific reasons for discontinuation may include, but are not restricted to, the following:
- intercurrent illness
- medical-significant adverse events (AEs), including AEs requiring emergency unblinding
- pregnancy
- protocol deviation or non-compliance
- termination of the study by the sponsor

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 January 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	30 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 7
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Croatia: 1
Country: Number of subjects enrolled	Czech Republic: 5
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Japan: 2
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	Russian Federation: 4
Country: Number of subjects enrolled	Turkey: 4

Country: Number of subjects enrolled	United States: 16
Worldwide total number of subjects	66
EEA total number of subjects	31

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)	24
Adolescents (12-17 years)	23
Adults (18-64 years)	19
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 56 study centers in 17 countries were initiated in this study. Participants were enrolled and treated at 41 centers in 16 countries, including 35 primary centers where participants initiated treatment and 6 qualified local medical centers where participants who were medically stable were transferred for long-term treatment.

Pre-assignment

Screening details:

To assess eligibility, participants were screened for a period of up to 6 weeks prior to enrollment in the study. A total of 86 participants were screened. Six of these participants underwent re-screening (of which 2 were eligible for the study). In total, 66 participants were eligible for the study and 20 participants were screen failures.

Period 1

Period 1 title	Double-blind Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Double-blind Sebelipase Alfa

Arm description:

Double-blind Period: Intravenous (IV) infusions of sebelipase alfa at a dose of 1 milligram/kilogram (mg/kg) administered once every other week (qow).

Arm type	Experimental
Investigational medicinal product name	Sebelipase alfa
Investigational medicinal product code	SBC-102
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Every other week IV infusions of sebelipase alfa at a dose of 1 mg/kg for 20 weeks.

Arm title	Double-blind Placebo

Arm description:

Double-blind Period: IV infusions of placebo administered qow.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Every other week IV infusions of matched placebo for 20 weeks.

Number of subjects in period 1	Double-blind Sebelipase Alfa	Double-blind Placebo
Started	36	30
Received at least 1 dose of study drug	36	30
Completed	35	30
Not completed	1	0
Adverse event, non-fatal	1	-

Period 2

Period 2 title	Open-label Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Open-label Sebelipase Alfa/Sebelipase Alfa

Arm description:

Participants who were randomized to receive sebelipase alfa during the Double-blind Period and also received sebelipase alfa in the Open-label Period. All participants received sebelipase alfa at a dose of 1 mg/kg qow, irrespective of treatment received in the Double-blind Period.

Arm type	Experimental
Investigational medicinal product name	Sebelipase alfa
Investigational medicinal product code	SBC-102
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Every other week IV infusions of sebelipase alfa at a dose of 1 mg/kg.

Arm title	Open-label Placebo/Sebelipase Alfa

Arm description:

Participants who were randomized to receive placebo during the Double-blind Period and received sebelipase alfa in the Open-label Period. All participants received sebelipase alfa at a dose of 1 mg/kg qow, irrespective of treatment received in the Double-blind Period.

Arm type	Experimental
Investigational medicinal product name	Sebelipase alfa
Investigational medicinal product code	SBC-102
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Every other week IV infusions of sebelipase alfa at a dose of 1 mg/kg.

Number of subjects in period 2	Open-label Sebelipase Alfa/Sebelipase Alfa	Open-label Placebo/Sebelipase Alfa
Started	35	30
Received at least 1 dose of study drug	36	30
Completed	34	29
Not completed	2	1
Consent withdrawn by subject	1	1
Lost to follow-up	1	-
Joined	1	0
Double-blind participant rechallenged	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Double-blind Sebelipase Alfa
Reporting group description:	
Double-blind Period: Intravenous (IV) infusions of sebelipase alfa at a dose of 1 milligram/kilogram (mg/kg) administered once every other week (qow).	
Reporting group title	Double-blind Placebo
Reporting group description:	
Double-blind Period: IV infusions of placebo administered qow.	

Reporting group values	Double-blind Sebelipase Alfa	Double-blind Placebo	Total
Number of subjects	36	30	66
Age categorical Units: Subjects			
Children (2-11 years)	14	10	24
Adolescents (12-17 years)	9	14	23
Adults (18-64 years)	13	6	19
Age continuous Units: years			
arithmetic mean	16.9	15.2	
standard deviation	± 11.6	± 10.2	-
Gender categorical Units: Subjects			
Female	18	15	33
Male	18	15	33
Ethnicity Units: Subjects			
Hispanic or Latino	6	4	10
Not Hispanic or Latino	30	26	56
Race Units: Subjects			
Asian	1	0	1
Japanese	2	0	2
Black or African American	1	0	1
White	27	28	55
Other	5	2	7

End points

End points reporting groups

Reporting group title	Double-blind Sebelipase Alfa
Reporting group description:	
Double-blind Period: Intravenous (IV) infusions of sebelipase alfa at a dose of 1 milligram/kilogram (mg/kg) administered once every other week (qow).	
Reporting group title	Double-blind Placebo
Reporting group description:	
Double-blind Period: IV infusions of placebo administered qow.	
Reporting group title	Open-label Sebelipase Alfa/Sebelipase Alfa
Reporting group description:	
Participants who were randomized to receive sebelipase alfa during the Double-blind Period and also received sebelipase alfa in the Open-label Period. All participants received sebelipase alfa at a dose of 1 mg/kg qow, irrespective of treatment received in the Double-blind Period.	
Reporting group title	Open-label Placebo/Sebelipase Alfa
Reporting group description:	
Participants who were randomized to receive placebo during the Double-blind Period and received sebelipase alfa in the Open-label Period. All participants received sebelipase alfa at a dose of 1 mg/kg qow, irrespective of treatment received in the Double-blind Period.	

Primary: Percentage Of Participants Achieving Alanine Aminotransferase Normalization

End point title	Percentage Of Participants Achieving Alanine Aminotransferase Normalization
End point description:	
Alanine Aminotransferase (ALT) normalization was defined as an abnormal baseline value (ALT > the age- and gender-specific upper limit of normal [ULN] provided by the central laboratory performing the assay) that becomes normal (< ULN). ALT normalization was evaluated at the end of the Double-blind Period (the last Double-blind assessment) and at the end of the Open-label Period (last Open-label assessment). Baseline for the Open-label Period was defined relative to the first infusion of sebelipase alfa, which occurred at Week 0 for participants in the sebelipase alfa/sebelipase alfa group and Week 22 for participants in the placebo/sebelipase alfa group. The last Open-label assessment varied by participant, depending on whether a participant completed treatment through Week 256 or discontinued prior to this timepoint to transition out of clinical study settings.	
End point type	Primary
End point timeframe:	
Double-blind Period: Baseline to the end of the Double-blind Period (Week 20). Open-label Period: Baseline to the last Open-label assessment (up to Week 256)	

End point values	Double-blind Sebelipase Alfa	Double-blind Placebo	Open-label Sebelipase Alfa/Sebelipase Alfa	Open-label Placebo/Sebelipase Alfa
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	36	30	36	30
Units: percentage of participants				
number (not applicable)	31	7	56	37

Statistical analyses

Statistical analysis title	Primary Analysis

Statistical analysis description:

A sample size of 50 randomised participants (approximately 25 participants per treatment group) provided 97% power to detect a statistically significant difference between sebelipase alfa and placebo, using Fisher's exact test at α=0.05.

Comparison groups	Double-blind Sebelipase Alfa v Double-blind Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0271
Method	Fisher exact

Secondary: Percent Change From Baseline In Low-density Lipoprotein Cholesterol (LDL-C)

End point title	Percent Change From Baseline In Low-density Lipoprotein Cholesterol (LDL-C)

End point description:

Relative reduction (percentage change from baseline) in LDL-C, as assessed by laboratory measurements was evaluated at the end of the Double-blind Period and at the end of the Open-label Period. Baseline for the Open-label Period was defined relative to the first infusion of sebelipase alfa, which occurred at Week 0 for participants in the sebelipase alfa/sebelipase alfa group and Week 22 for participants in the placebo/sebelipase alfa group. The last Open-label assessment varied by participant, depending on whether a participant completed treatment through Week 256 or discontinued prior to this timepoint to transition out of clinical study settings.

End point type	Secondary

End point timeframe:

Double-blind Period: Baseline to the end of the Double-blind Period (Week 20). Open-label Period: Baseline to the last Open-label assessment (up to Week 256).

End point values	Double-blind Sebelipase Alfa	Double-blind Placebo	Open-label Sebelipase Alfa/Sebelipase Alfa	Open-label Placebo/Sebelipase Alfa
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	36	30	36	30
Units: percent change				
arithmetic mean (standard deviation)	-28.42 (± 22.304)	-6.25 (± 13.015)	-19.74 (± 33.262)	-18.09 (± 33.685)

Statistical analyses

Statistical analysis title	Secondary efficacy endpoint
Comparison groups	Double-blind Sebelipase Alfa v Double-blind Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Secondary: Percent Change From Baseline In Non-high Density Lipoprotein Cholesterol (Non-HDL-C)

End point title	Percent Change From Baseline In Non-high Density Lipoprotein Cholesterol (Non-HDL-C)

End point description:

Relative reduction (percent change from baseline) in non-HDL-C, as assessed by laboratory measurements, was evaluated at the end of the Double-blind Period and the Open-label Period. Baseline for the Open-label Period was defined relative to the first infusion of sebelipase alfa, which occurred at Week 0 for participants in the sebelipase alfa/sebelipase alfa group and Week 22 for participants in the placebo/sebelipase alfa group. The last Open-label assessment varied by participant, depending on whether a participant completed treatment through Week 256 or discontinued prior to this timepoint to transition out of clinical study settings.

End point type	Secondary

End point timeframe:

Double-blind Period: Baseline to the end of the Double-blind Period (Week 20). Open-label Period: Baseline to the last Open-label assessment (up to Week 256).

End point values	Double-blind Sebelipase Alfa	Double-blind Placebo	Open-label Sebelipase Alfa/Sebelipase Alfa	Open-label Placebo/Sebelipase Alfa
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	36	30	36	30
Units: percent change				
arithmetic mean (standard deviation)	-27.97 (± 18.612)	-6.94 (± 10.922)	-19.75 (± 26.875)	-18.34 (± 29.177)

Statistical analyses

Statistical analysis title	Secondary efficacy endpoint
Comparison groups	Double-blind Sebelipase Alfa v Double-blind Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Secondary: Percentage Of Participants Achieving Aspartate Aminotransferase Normalization

End point title	Percentage Of Participants Achieving Aspartate Aminotransferase Normalization

End point description:

Aspartate Aminotransferase (AST) normalization was defined as an abnormal baseline value (AST > the age- and gender-specific ULN provided by the central laboratory performing the assay) that becomes normal (< ULN). AST normalization was evaluated at the end of the Double-blind Period (the last Double-blind assessment) and at the end of the Open-label Period (last Open-label assessment). Baseline for the Open-label Period was defined relative to the first infusion of sebelipase alfa, which occurred at Week 0 for participants in the sebelipase alfa/sebelipase alfa group and Week 22 for participants in the placebo/sebelipase alfa group. The last Open-label assessment varied by participant, depending on whether a participant completed treatment through Week 256 or discontinued prior to this timepoint to transition out of clinical study settings.

End point type	Secondary

End point timeframe:

Double-blind Period: Baseline to the end of the Double-blind Period (Week 20). Open-label Period: Baseline to the last Open-label assessment (up to Week 256).

End point values	Double-blind Sebelipase Alfa	Double-blind Placebo	Open-label Sebelipase Alfa/Sebelipase Alfa	Open-label Placebo/Sebelipase Alfa
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	36	29	36	29
Units: Percentage Of Participants				
number (not applicable)	42	3	69	62

Statistical analyses

Statistical analysis title	Secondary efficacy endpoint
Comparison groups	Double-blind Sebelipase Alfa v Double-blind Placebo
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	Fisher exact

Secondary: Percent Change From Baseline In Triglycerides

End point title	Percent Change From Baseline In Triglycerides

End point description:

Relative reduction (percent change from baseline) in triglycerides, as assessed by laboratory measurements, was evaluated at the end of the Double-blind Period and the Open-label Period. Baseline for the Open-label Period was defined relative to the first infusion of sebelipase alfa, which occurred at Week 0 for participants in the sebelipase alfa/sebelipase alfa group and Week 22 for participants in the

placebo/sebelipase alfa group. The last Open-label assessment varied by participant, depending on whether a participant completed treatment through Week 256 or discontinued prior to this timepoint to transition out of clinical study settings.

End point type	Secondary

End point timeframe:

Double-blind Period: Baseline to the end of the Double-blind Period (Week 20). Open-label Period: Baseline to the last Open-label assessment (up to Week 256).

End point values	Double-blind Sebelipase Alfa	Double-blind Placebo	Open-label Sebelipase Alfa/Sebelipase Alfa	Open-label Placebo/Sebelipase Alfa
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	36	30	36	30
Units: percent change				
arithmetic mean (standard deviation)	-25.45 (± 29.411)	-11.14 (± 28.827)	-11.87 (± 34.580)	-19.63 (± 27.066)

Statistical analyses

Statistical analysis title	Secondary efficacy endpoint
Comparison groups	Double-blind Sebelipase Alfa v Double-blind Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0375
Method	Wilcoxon (Mann-Whitney)

Secondary: Percent Change From Baseline In High-density Lipoprotein Cholesterol (HDL-C)

End point title	Percent Change From Baseline In High-density Lipoprotein Cholesterol (HDL-C)

End point description:

Relative increase (percent change from baseline) in HDL-C, assessed by laboratory measurements, was evaluated at the end of the Double-blind Period and the Open-label Period. Baseline for the Open-label Period was defined relative to the first infusion of sebelipase alfa, which occurred at Week 0 for participants in the sebelipase alfa/sebelipase alfa group and Week 22 for participants in the placebo/sebelipase alfa group. The last Open-label assessment varied by participant, depending on whether a participant completed treatment through Week 256 or discontinued prior to this timepoint to transition out of clinical study settings.

End point type	Secondary

End point timeframe:

Double-blind Period: Baseline to the end of the Double-blind Period (Week 20). Open-label Period: Baseline to the last Open-label assessment (up to Week 256).

End point values	Double-blind Sebelipase Alfa	Double-blind Placebo	Open-label Sebelipase Alfa/Sebelipase Alfa	Open-label Placebo/Sebelipase Alfa
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	36	30	36	30
Units: percent change				
arithmetic mean (standard deviation)	19.57 (± 16.833)	-0.29 (± 12.36)	31.65 (± 28.971)	34.78 (± 29.927)

Statistical analyses

Statistical analysis title	Secondary efficacy endpoint
Comparison groups	Double-blind Sebelipase Alfa v Double-blind Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)
Variability estimate	Standard deviation

Secondary: Percent Change From Baseline In Liver Fat Content

End point title	Percent Change From Baseline In Liver Fat Content

End point description:

Decrease in liver fat content, as assessed by magnetic resonance imaging (MRI), was evaluated in participants for whom imaging was performed. Baseline for the Open-label Period was defined relative to the first infusion of sebelipase alfa, which occurred at Week 0 for participants in the sebelipase alfa/sebelipase alfa group and Week 22 for participants in the placebo/sebelipase alfa group. The last Open-label assessment varied by participant, depending on whether a participant completed treatment through Week 256 or discontinued prior to this timepoint to transition out of clinical study settings.

End point type	Secondary

End point timeframe:

Double-blind Period: Baseline to the end of the Double-blind Period (Week 20). Open-label Period: Baseline to the last Open-label assessment (up to Week 256).

End point values	Double-blind Sebelipase Alfa	Double-blind Placebo	Open-label Sebelipase Alfa/Sebelipase Alfa	Open-label Placebo/Sebelipase Alfa
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	25	35	25
Units: percent change				
arithmetic mean (standard deviation)	-31.98 (± 26.763)	-4.21 (± 15.559)	-9.89 (± 32.892)	-0.93 (± 37.233)

Statistical analyses

Statistical analysis title	Secondary efficacy endpoint
Comparison groups	Double-blind Sebelipase Alfa v Double-blind Placebo
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Secondary: Participants With Improvement In Liver Histopathology (Decrease Of >5% In Hepatic Steatosis Score)

End point title	Participants With Improvement In Liver Histopathology (Decrease Of >5% In Hepatic Steatosis Score)

End point description:

The number of participants who had an improvement in hepatic histopathology (a decrease of >5% in hepatic steatosis score), as determined by blinded central review, in the participants for whom liver biopsy was performed. Baseline for the Open-label Period was defined relative to the first infusion of sebelipase alfa, which occurred at Week 0 for participants in the sebelipase alfa/sebelipase alfa group and Week 22 for participants in the placebo/sebelipase alfa group.

End point type	Secondary

End point timeframe:

Double-blind Period: Baseline to the end of the Double-blind Period (Week 20). Open-label Period: Baseline up to Week 52.

End point values	Double-blind Sebelipase Alfa	Double-blind Placebo	Open-label Sebelipase Alfa/Sebelipase Alfa	Open-label Placebo/Sebelipase Alfa
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	10	12	6
Units: participants	10	4	7	4

Statistical analyses

Statistical analysis title	Secondary efficacy endpoint
Comparison groups	Double-blind Sebelipase Alfa v Double-blind Placebo
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4216
Method	Fisher exact

Secondary: Percent Change From Baseline In Liver Volume

End point title	Percent Change From Baseline In Liver Volume

End point description:

Relative reduction (percent change from baseline) in liver volume, as assessed by MRI, was evaluated in participants for whom imaging was performed. Baseline for the Open-label Period was defined relative to the first infusion of sebelipase alfa, which occurred at Week 0 for participants in the sebelipase alfa/sebelipase alfa group and Week 22 for participants in the placebo/sebelipase alfa group. The last Open-label assessment varied by participant, depending on whether a participant completed treatment through Week 256 or discontinued prior to this timepoint to transition out of clinical study settings.

End point type	Secondary

End point timeframe:

Double-blind Period: Baseline to the end of the Double-blind Period (Week 20). Open-label Period: Baseline to the last Open-label assessment (up to Week 256).

End point values	Double-blind Sebelipase Alfa	Double-blind Placebo	Open-label Sebelipase Alfa/Sebelipase Alfa	Open-label Placebo/Sebelipase Alfa
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33	27	36	27
Units: percent change				
arithmetic mean (standard deviation)	-10.28 (± 10.51)	-2.66 (± 10.107)	-24.04 (± 15.792)	-21.55 (± 11.727)

Statistical analyses

Statistical analysis title	Secondary efficacy endpoint
Comparison groups	Double-blind Sebelipase Alfa v Double-blind Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0068
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Double-blind Period: AEs assessed on or after first infusion of study drug until Week 20. Open-label Period: AEs assessed after first infusion of study drug on Week 22 up to follow-up call (4 weeks [+7 days] after the last infusion).

Adverse event reporting additional description:

Adverse events were obtained through spontaneous reporting or were elicited by specific questioning of the participant or the participant's parent or legal guardian.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Double-blind Sebelipase Alfa

Reporting group description:

Double-blind Period: IV infusions of sebelipase alfa at a dose of 1 mg/kg administered qow.

Reporting group title	Double-blind Placebo

Reporting group description:

Double-blind Period: IV infusions of placebo administered qow.

Reporting group title	Open-label Sebelipase Alfa/Sebelipase Alfa

Reporting group description:

Participants who were randomized to receive sebelipase alfa during the Double-blind Period and also received sebelipase alfa in the Open-label Period. All participants received sebelipase alfa at a dose of 1 mg/kg qow, irrespective of treatment received in the Double-blind Period.

Reporting group title	Open-label Placebo/Sebelipase Alfa

Reporting group description:

Participants who were randomized to receive placebo during the Double-blind Period and received sebelipase alfa in the Open-label Period. All participants received sebelipase alfa at a dose of 1 mg/kg qow, irrespective of treatment received in the Double-blind Period.

Serious adverse events	Double-blind Sebelipase Alfa	Double-blind Placebo	Open-label Sebelipase Alfa/Sebelipase Alfa
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 36 (5.56%)	1 / 30 (3.33%)	6 / 36 (16.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatic cancer			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lung			

subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	2 / 36 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hyperaemia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Epilepsy			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic encephalopathy			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Road traffic accident			
subjects affected / exposed	0 / 36 (0.00%)	1 / 30 (3.33%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest discomfort			

subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Infusion related reaction			
subjects affected / exposed	1 / 36 (2.78%)	0 / 30 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Eyelid oedema			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 36 (2.78%)	0 / 30 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sleep apnoea syndrome			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Pruritus			

subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patellofemoral pain syndrome			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Plantar fasciitis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 36 (2.78%)	0 / 30 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Peritonitis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Open-label Placebo/Sebelipase Alfa		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 30 (16.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatic cancer			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metastases to lung			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Procedural pain			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hyperaemia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Epilepsy			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic encephalopathy			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Road traffic accident			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chest discomfort			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Infusion related reaction			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Eyelid oedema			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sleep apnoea syndrome			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Urticaria			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Patellofemoral pain syndrome			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Plantar fasciitis			

subjects affected / exposed	0 / 30 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peritonitis			
subjects affected / exposed	1 / 30 (3.33%)		
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	Double-blind Sebelipase Alfa	Double-blind Placebo	Open-label Sebelipase Alfa/Sebelipase Alfa
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 36 (86.11%)	28 / 30 (93.33%)	35 / 36 (97.22%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 36 (2.78%)	0 / 30 (0.00%)	2 / 36 (5.56%)
occurrences (all)	1	0	2
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	7 / 36 (19.44%)	6 / 30 (20.00%)	15 / 36 (41.67%)
occurrences (all)	7	6	20

Asthenia			
subjects affected / exposed	3 / 36 (8.33%)	1 / 30 (3.33%)	1 / 36 (2.78%)
occurrences (all)	3	1	1
Fatigue			
subjects affected / exposed	0 / 36 (0.00%)	2 / 30 (6.67%)	3 / 36 (8.33%)
occurrences (all)	0	2	3
Vaccination site pain			
subjects affected / exposed	0 / 36 (0.00%)	2 / 30 (6.67%)	0 / 36 (0.00%)
occurrences (all)	0	2	0
Chest pain			
subjects affected / exposed	1 / 36 (2.78%)	0 / 30 (0.00%)	1 / 36 (2.78%)
occurrences (all)	1	0	1
Malaise			
subjects affected / exposed	0 / 36 (0.00%)	1 / 30 (3.33%)	2 / 36 (5.56%)
occurrences (all)	0	1	2
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	4 / 36 (11.11%)
occurrences (all)	0	0	7
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed[1]	0 / 18 (0.00%)	1 / 15 (6.67%)	3 / 18 (16.67%)
occurrences (all)	0	1	6
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	6 / 36 (16.67%)	1 / 30 (3.33%)	5 / 36 (13.89%)
occurrences (all)	8	1	8
Epistaxis			
subjects affected / exposed	4 / 36 (11.11%)	6 / 30 (20.00%)	5 / 36 (13.89%)
occurrences (all)	8	7	24
Cough			
subjects affected / exposed	3 / 36 (8.33%)	3 / 30 (10.00%)	12 / 36 (33.33%)
occurrences (all)	3	4	30
Rhinorrhoea			
subjects affected / exposed	2 / 36 (5.56%)	1 / 30 (3.33%)	8 / 36 (22.22%)
occurrences (all)	2	1	25

Asthma			
subjects affected / exposed	1 / 36 (2.78%)	0 / 30 (0.00%)	2 / 36 (5.56%)
occurrences (all)	1	0	3
Rhinitis allergic			
subjects affected / exposed	1 / 36 (2.78%)	0 / 30 (0.00%)	4 / 36 (11.11%)
occurrences (all)	1	0	4
Nasal congestion			
subjects affected / exposed	0 / 36 (0.00%)	1 / 30 (3.33%)	5 / 36 (13.89%)
occurrences (all)	0	1	5
Productive cough			
subjects affected / exposed	1 / 36 (2.78%)	0 / 30 (0.00%)	0 / 36 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 36 (5.56%)	0 / 30 (0.00%)	2 / 36 (5.56%)
occurrences (all)	2	0	2
Autism spectrum disorder			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2
Sleep disorder			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	0 / 36 (0.00%)
occurrences (all)	0	0	0
Investigations			
Body temperature increased			
subjects affected / exposed	2 / 36 (5.56%)	1 / 30 (3.33%)	0 / 36 (0.00%)
occurrences (all)	4	1	0
Blood cholesterol increased			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2
Blood pressure increased			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2
Cardiac murmur			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2
Eosinophil count increased			

subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	0 / 36 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Procedural pain	Additional description: Procedural pain after liver biopsy unrelated to study drug		
subjects affected / exposed	1 / 36 (2.78%)	3 / 30 (10.00%)	0 / 36 (0.00%)
occurrences (all)	1	3	0
Ligament sprain			
subjects affected / exposed	1 / 36 (2.78%)	1 / 30 (3.33%)	4 / 36 (11.11%)
occurrences (all)	2	1	6
Contusion			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	5 / 36 (13.89%)
occurrences (all)	0	0	5
Skin abrasion			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	4 / 36 (11.11%)
occurrences (all)	0	0	5
Arthropod bite			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	3
Laceration			
subjects affected / exposed	0 / 36 (0.00%)	1 / 30 (3.33%)	2 / 36 (5.56%)
occurrences (all)	0	1	3
Thermal burn			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2
Joint injury			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2
Sunburn			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 36 (0.00%)	2 / 30 (6.67%)	0 / 36 (0.00%)
occurrences (all)	0	2	0
Nervous system disorders			

Headache			
subjects affected / exposed	10 / 36 (27.78%)	6 / 30 (20.00%)	19 / 36 (52.78%)
occurrences (all)	17	7	56
Syncope			
subjects affected / exposed	2 / 36 (5.56%)	0 / 30 (0.00%)	1 / 36 (2.78%)
occurrences (all)	2	0	2
Dizziness			
subjects affected / exposed	0 / 36 (0.00%)	1 / 30 (3.33%)	6 / 36 (16.67%)
occurrences (all)	0	2	8
Somnolence			
subjects affected / exposed	1 / 36 (2.78%)	1 / 30 (3.33%)	1 / 36 (2.78%)
occurrences (all)	1	1	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2
Eosinophilia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 36 (16.67%)	5 / 30 (16.67%)	7 / 36 (19.44%)
occurrences (all)	6	6	13
Abdominal pain			
subjects affected / exposed	3 / 36 (8.33%)	1 / 30 (3.33%)	7 / 36 (19.44%)
occurrences (all)	4	1	10
Constipation			
subjects affected / exposed	3 / 36 (8.33%)	1 / 30 (3.33%)	4 / 36 (11.11%)
occurrences (all)	3	1	4
Nausea			
subjects affected / exposed	3 / 36 (8.33%)	2 / 30 (6.67%)	5 / 36 (13.89%)
occurrences (all)	3	2	7
Vomiting			

subjects affected / exposed	3 / 36 (8.33%)	3 / 30 (10.00%)	9 / 36 (25.00%)
occurrences (all)	4	6	17
Abdominal pain upper			
subjects affected / exposed	2 / 36 (5.56%)	2 / 30 (6.67%)	10 / 36 (27.78%)
occurrences (all)	3	2	13
Odynophagia			
subjects affected / exposed	0 / 36 (0.00%)	1 / 30 (3.33%)	2 / 36 (5.56%)
occurrences (all)	0	1	6
Toothache			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	10
Ascites			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	8
Abdominal discomfort			
subjects affected / exposed	0 / 36 (0.00%)	1 / 30 (3.33%)	1 / 36 (2.78%)
occurrences (all)	0	1	1
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 36 (2.78%)	0 / 30 (0.00%)	1 / 36 (2.78%)
occurrences (all)	1	0	1
Gastritis			
subjects affected / exposed	1 / 36 (2.78%)	0 / 30 (0.00%)	2 / 36 (5.56%)
occurrences (all)	1	0	3
Eructation			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	0 / 36 (0.00%)
occurrences (all)	0	0	0
Gingival bleeding			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	0 / 36 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 36 (2.78%)	3 / 30 (10.00%)	2 / 36 (5.56%)
occurrences (all)	3	4	3
Urticaria			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	3 / 36 (8.33%)
occurrences (all)	0	0	3

Dermatitis allergic			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	0 / 36 (0.00%)
occurrences (all)	0	0	0
Ecchymosis			
subjects affected / exposed	1 / 36 (2.78%)	0 / 30 (0.00%)	1 / 36 (2.78%)
occurrences (all)	1	0	1
Dermatitis atopic			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	4
Eczema			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	1 / 36 (2.78%)	0 / 30 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Dermatitis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 36 (5.56%)	1 / 30 (3.33%)	3 / 36 (8.33%)
occurrences (all)	2	1	3
Musculoskeletal pain			
subjects affected / exposed	1 / 36 (2.78%)	0 / 30 (0.00%)	3 / 36 (8.33%)
occurrences (all)	1	0	3
Back pain			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	5
Osteoporosis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2
Neck pain			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	0 / 36 (0.00%)
occurrences (all)	0	0	0
Tendonitis			

subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2
Pain in extremity			
subjects affected / exposed	1 / 36 (2.78%)	0 / 30 (0.00%)	3 / 36 (8.33%)
occurrences (all)	1	0	4
Myalgia			
subjects affected / exposed	0 / 36 (0.00%)	1 / 30 (3.33%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	6 / 36 (16.67%)	6 / 30 (20.00%)	10 / 36 (27.78%)
occurrences (all)	8	7	25
Nasopharyngitis			
subjects affected / exposed	4 / 36 (11.11%)	3 / 30 (10.00%)	17 / 36 (47.22%)
occurrences (all)	4	3	61
Sinusitis			
subjects affected / exposed	2 / 36 (5.56%)	0 / 30 (0.00%)	4 / 36 (11.11%)
occurrences (all)	2	0	4
Rhinitis			
subjects affected / exposed	2 / 36 (5.56%)	3 / 30 (10.00%)	4 / 36 (11.11%)
occurrences (all)	2	3	7
Tonsillitis			
subjects affected / exposed	2 / 36 (5.56%)	4 / 30 (13.33%)	4 / 36 (11.11%)
occurrences (all)	2	4	5
Pharyngitis			
subjects affected / exposed	0 / 36 (0.00%)	5 / 30 (16.67%)	6 / 36 (16.67%)
occurrences (all)	0	5	7
Respiratory tract infection viral			
subjects affected / exposed	0 / 36 (0.00%)	2 / 30 (6.67%)	0 / 36 (0.00%)
occurrences (all)	0	2	0
Varicella			
subjects affected / exposed	0 / 36 (0.00%)	3 / 30 (10.00%)	1 / 36 (2.78%)
occurrences (all)	0	2	1
Respiratory tract infection			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	3 / 36 (8.33%)
occurrences (all)	0	0	8

Gastroenteritis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	5 / 36 (13.89%)
occurrences (all)	0	0	5
Bronchitis			
subjects affected / exposed	0 / 36 (0.00%)	1 / 30 (3.33%)	2 / 36 (5.56%)
occurrences (all)	0	1	3
Influenza			
subjects affected / exposed	0 / 36 (0.00%)	1 / 30 (3.33%)	3 / 36 (8.33%)
occurrences (all)	0	1	3
Urinary tract infection			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2
Conjunctivitis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Oral herpes			
subjects affected / exposed	1 / 36 (2.78%)	0 / 30 (0.00%)	1 / 36 (2.78%)
occurrences (all)	1	0	1
Vulvovaginitis			
subjects affected / exposed[2]	0 / 36 (0.00%)	0 / 30 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Otitis media			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	3 / 36 (8.33%)
occurrences (all)	0	0	3
Viral infection			
subjects affected / exposed	0 / 36 (0.00%)	1 / 30 (3.33%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis viral			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	0 / 36 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal infection			
subjects affected / exposed	1 / 36 (2.78%)	0 / 30 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Ear infection			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2

Rotavirus infection			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	0 / 36 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Vitamin D deficiency			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	8 / 36 (22.22%)
occurrences (all)	0	0	11
Iron deficiency			
subjects affected / exposed	0 / 36 (0.00%)	0 / 30 (0.00%)	3 / 36 (8.33%)
occurrences (all)	0	0	3

Non-serious adverse events	Open-label Placebo/Sebelipase Alfa		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 30 (96.67%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	9 / 30 (30.00%)		
occurrences (all)	18		
Asthenia			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Vaccination site pain			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Chest pain			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	7		
Malaise			

subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	3		
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	3		
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed[1]	4 / 15 (26.67%)		
occurrences (all)	21		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	6 / 30 (20.00%)		
occurrences (all)	16		
Epistaxis			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	9		
Cough			
subjects affected / exposed	9 / 30 (30.00%)		
occurrences (all)	19		
Rhinorrhoea			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	9		
Asthma			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	12		
Rhinitis allergic			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	7		
Nasal congestion			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Productive cough			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	3		
Psychiatric disorders			

Anxiety			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Autism spectrum disorder			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Sleep disorder			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Investigations			
Body temperature increased			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Blood cholesterol increased			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Blood pressure increased			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Cardiac murmur			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Eosinophil count increased			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Procedural pain	Additional description: Procedural pain after liver biopsy unrelated to study drug		
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	2		
Ligament sprain			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	6		
Contusion			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Skin abrasion			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Arthropod bite			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Laceration			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Thermal burn			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Joint injury			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Sunburn			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 30 (40.00%)		
occurrences (all)	33		
Syncope			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Somnolence			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	4		
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Eosinophilia			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	11 / 30 (36.67%)		
occurrences (all)	20		
Abdominal pain			
subjects affected / exposed	9 / 30 (30.00%)		
occurrences (all)	21		
Constipation			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	5		
Nausea			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	4		
Vomiting			
subjects affected / exposed	7 / 30 (23.33%)		
occurrences (all)	14		
Abdominal pain upper			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Odynophagia			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	8		
Toothache			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	3		
Ascites			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Abdominal discomfort			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	5		
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Gastritis			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Eructation			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Gingival bleeding			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	4		
Urticaria			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	14		
Dermatitis allergic			
subjects affected / exposed	6 / 30 (20.00%)		
occurrences (all)	12		
Ecchymosis			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	9		
Dermatitis atopic			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	3		
Eczema			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	3		

Pruritus			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Dermatitis			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	9		
Musculoskeletal pain			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	3		
Back pain			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Osteoporosis			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Neck pain			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Tendonitis			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	9		
Nasopharyngitis			

subjects affected / exposed	14 / 30 (46.67%)			
occurrences (all)	28			
Sinusitis				
subjects affected / exposed	0 / 30 (0.00%)			
occurrences (all)	0			
Rhinitis				
subjects affected / exposed	9 / 30 (30.00%)			
occurrences (all)	17			
Tonsillitis				
subjects affected / exposed	3 / 30 (10.00%)			
occurrences (all)	3			
Pharyngitis				
subjects affected / exposed	5 / 30 (16.67%)			
occurrences (all)	8			
Respiratory tract infection viral				
subjects affected / exposed	4 / 30 (13.33%)			
occurrences (all)	16			
Varicella				
subjects affected / exposed	0 / 30 (0.00%)			
occurrences (all)	0			
Respiratory tract infection				
subjects affected / exposed	5 / 30 (16.67%)			
occurrences (all)	20			
Gastroenteritis				
subjects affected / exposed	7 / 30 (23.33%)			
occurrences (all)	11			
Bronchitis				
subjects affected / exposed	3 / 30 (10.00%)			
occurrences (all)	3			
Influenza				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences (all)	2			
Urinary tract infection				
subjects affected / exposed	2 / 30 (6.67%)			
occurrences (all)	3			
Conjunctivitis				

subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Oral herpes			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Vulvovaginitis			
subjects affected / exposed[2]	2 / 15 (13.33%)		
occurrences (all)	2		
Otitis media			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Viral infection			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Gastroenteritis viral			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	3		
Gastrointestinal infection			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	3		
Ear infection			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Rotavirus infection			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Vitamin D deficiency			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	4		
Iron deficiency			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Adverse event occurring in female participants only.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Adverse event occurring in female participants only.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 January 2015	• Modified the antidrug antibodies (ADA) safety endpoint to remove characterization of seroconversion and tolerization. • Clarified that lysosomal acid lipase enzyme activity and deoxyribonucleic acid (DNA) blood sampling would not be repeated if a participant underwent rescreening. • Added assessments of selected laboratory parameters before and/or after any dose change or change in lipid-lowering medication (LLM). • Clarified that the blood sample for the liver panel should be obtained before the liver biopsy due to the potential of a transient elevation of hepatic transaminases after a liver biopsy. • Allowed the dose (mg) of sebelipase alfa to be determined based on a participant's last available weight measurement if weight could not be obtained on the day of the infusion due to the participant's condition. • Replaced "inadequate clinical response" with "criteria for dose escalation," as dose escalation may also be required for persistent disease progression. • Replaced "infusion related reaction" with "infusion-associated reaction. • Updated the guidance on management of infusion-associated reactions. • Updated and clarified safety reporting timelines.
16 March 2015	•Modified the safety endpoint for immunogenicity to remove reference to seroconversion and tolerization. • Added clarifications: Screening assessments of LAL enzyme activity and DNA sampling did not need to be repeated if a participant rescreened for the study; the blood sample for the liver panel should be obtained before the liver biopsy due to the potential of a transient elevation of hepatic transaminases after a liver biopsy. • In the dose escalation criteria, added criteria for "significant clinical progression of liver disease." Also removed the term "inadequate clinical response" when describing dose escalation criteria, as dose escalation may be required for persistent disease progression as well as inadequate clinical response. • Added collection of blood sample for selected laboratory tests in participants who had a dose modification or a change in LLM. • Added the following for the first 12 weeks after a dose increase: Vital sign monitoring was extended to 2 hours postinfusion (if the participant had been previously approved for a decrease in postinfusion vital sign monitoring); recommended that the infusion should be administered over 2 hours; participants previously on home infusion were required to return to study site for infusions and follow dose escalation recommendations for laboratory assessments and vital sign collection. • Corrected the study duration from 150 to 152 weeks (to account for the 2 weeks between the end of the Double-blind Period at Week 20 and the beginning of the Open-label Extension Period at Week 22). • In Schedule of Assessments, indicated that the screening period extended to Day 0, and that carbohydrate deficient transferrin should be assessed preinfusion at Week 0. • Allowed the dose (mg) of sebelipase alfa to be determined based on a participant's last available weight measurement if weight could not be obtained on the day of the infusion due to the participant's condition. • Updated safety reporting information.

20 November 2015	• Added a 104 week Open-label Expanded Treatment Period, to ensure that all participants continue to have access to treatment until sebelipase alfa is registered and available in their study region. • Added an additional liver biopsy during long-term treatment in the Open-label Extension Period. This biopsy could be obtained on an optional basis between Week 104 and Week 152. • Added serial pharmacokinetics assessments and a predose ADA assessment for participants who received a dose modification, to be performed at the time of the first infusion at the new dose/schedule.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported