Clinical trial results:
A Multicenter, Open-Label Study of Sebelipase Alfa in Patients with Lysosomal Acid Lipase Deficiency

Summary

EudraCT number	2011-004287-30
Trial protocol	DK ES GB IT DE BE HR NL
Global end of trial date	28 December 2017

Results information

Result version number	v2
This version publication date	24 February 2019
First version publication date	21 July 2018
Version creation reason	• New data added to full data set This update includes new data and changes in presentation of current data. All new data originates from the same clinical study report source as the original posting. The new data involves end point 5, with new/different data to accommodate the change in end point title. Changes in presentation of data for the Subject disposition and the Adverse events (AEs) were respectively made to provide a more clear account of the study's variable dosing and to ensure presentation of AEs per intervention.

Trial information

Trial identification

Sponsor protocol code	LAL-CL06

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02112994
WHO universal trial number (UTN)	U1111-1152-7171

Notes:

Sponsors

Sponsor organisation name	Alexion Pharmaceuticals Inc.
Sponsor organisation address	100 College St., New Haven, United States, 06510
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	16 April 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the safety and efficacy of sebelipase alfa in a broad population of participants with lysosomal acid lipase deficiency.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 June 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	Croatia: 2
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Brazil: 2
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	Russian Federation: 1
Country: Number of subjects enrolled	Turkey: 1
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	31
EEA total number of subjects	18

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)	16
Adolescents (12-17 years)	6
Adults (18-64 years)	9
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 21 study centers were initiated in 15 countries, including Australia, Belgium, Brazil, Canada, Croatia, Denmark, Germany, Italy, Mexico, Netherlands, Russia, Spain, Turkey, United Kingdom (UK), and the United States. Seventeen study centers screened at least 1 participant in all of these countries, except the UK and the Netherlands.

Pre-assignment

Screening details:

The study consisted of a screening period of up to 45 days. The maximum duration of a participant's participation in the study, inclusive of screening and follow-up visits, was approximately 155 weeks.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

None (Open Label)

Arms

Are arms mutually exclusive?	Yes
Arm title	2-<4 Years

Arm description:

This subgroup is part of the full analysis set and includes only participants between the ages of 2 and 4 years old who initiated intravenous (IV) treatment with sebelipase alfa at a dose of 1 milligram/kilogram (mg/kg) every other week (qow). Participants were considered for a dose adjustment at the discretion of the Investigator and in consultation with the Sponsor. Dose escalation to 3 mg/kg qow was considered if pre-defined dose-escalation criteria were met. If these criteria continued to be met, a subsequent dose escalation to 3 mg/kg every week (qw) was considered. Dose decreases as low as 0.35 mg/kg qow were permitted based upon evidence of intolerance to sebelipase alfa treatment. Participants who completed the 96-week treatment period were permitted to continue receiving sebelipase alfa in an expanded treatment period for up to 48 weeks, pending local drug availability and study participation status.

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

Dosage and administration details:

All eligible participants received repeat IV infusions of sebelipase alfa at an initial dose of 1 mg/kg qow. Sequential dose escalation to 3 mg/kg qow and 3 mg/kg qw was permitted based on evidence of disease progression. Dose decreases were permitted in the event of poor tolerability or in participants who achieved clinical stability on a dose of 3 mg/kg qw. Consecutive infusions were to be administered at least 7 days apart (for qow dosing) and at least 5 days apart (qw dosing).

Arm title	4-18 Years

Arm description:

This subgroup is part of the full analysis set and includes only participants between the ages of 4 and 18 years old who initiated IV treatment with sebelipase alfa at a dose of 1 mg/kg qow. Participants were considered for a dose adjustment at the discretion of the Investigator and in consultation with the Sponsor. Dose escalation to 3 mg/kg qow was considered if pre-defined dose-escalation criteria were met. If these criteria continued to be met, a subsequent dose escalation to 3 mg/kg qw was considered. Dose decreases as low as 0.35 mg/kg qow were permitted based upon evidence of intolerance to sebelipase alfa treatment. Participants who completed the 96-week treatment period were permitted to continue receiving sebelipase alfa in an expanded treatment period for up to 48 weeks, pending local

drug availability and study participation status.

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

Dosage and administration details:

All eligible participants received repeat IV infusions of sebelipase alfa at an initial dose of 1 mg/kg qow. Sequential dose escalation to 3 mg/kg qow and 3 mg/kg qw was permitted based on evidence of disease progression. Dose decreases were permitted in the event of poor tolerability or in participants who achieved clinical stability on a dose of 3 mg/kg qw. Consecutive infusions were to be administered at least 7 days apart (for qow dosing) and at least 5 days apart (qw dosing).

Arm title	>18 Years

Arm description:

This subgroup is part of the full analysis set and includes only participants greater than 18 years old who initiated IV treatment with sebelipase alfa at a dose of 1 mg/kg qow. Participants were considered for a dose adjustment at the discretion of the Investigator and in consultation with the Sponsor. Dose escalation to 3 mg/kg qow was considered if pre-defined dose-escalation criteria were met. If these criteria continued to be met, a subsequent dose escalation to 3 mg/kg qw was considered. Dose decreases as low as 0.35 mg/kg qow were permitted based upon evidence of intolerance to sebelipase alfa treatment. Participants who completed the 96-week treatment period were permitted to continue receiving sebelipase alfa in an expanded treatment period for up to 48 weeks, pending local drug availability and study participation status.

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

Dosage and administration details:

All eligible participants received repeat IV infusions of sebelipase alfa at an initial dose of 1 mg/kg qow. Sequential dose escalation to 3 mg/kg qow and 3 mg/kg qw was permitted based on evidence of disease progression. Dose decreases were permitted in the event of poor tolerability or in participants who achieved clinical stability on a dose of 3 mg/kg qw. Consecutive infusions were to be administered at least 7 days apart (for qow dosing) and at least 5 days apart (qw dosing).

Number of subjects in period 1	2-<4 Years	4-18 Years	>18 Years
Started	6	16	9
Received at Least 1 Dose of Study Drug	6	16	9
Received 0.35 mg/kg qow	0 [1]	0 [2]	1 [3]
Received 1 mg/kg qow	6	16	9
Received 1 mg/kg qw	1 [4]	1 [5]	0 [6]
Received 3 mg/kg qow	3 [7]	5 [8]	3 [9]
Received 3 mg/kg qw	2 [10]	1 [11]	1 [12]
Completed 96-week Treatment Period	6	14	8
Completed	6	13	6
Not completed	0	3	3
Consent withdrawn by subject	-	1	1

Liver Transplant	-	1	-
Progressive Disease	-	-	1
Pregnancy	-	1	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This Milestone represents 1 of the 5 different doses of the study. Dosing was variable and on an individual, per participant basis. All participants began treatment with the study drug at a dose of 1 mg/kg every other week. Dose escalations/reductions could be considered if the participant met protocol-defined criteria. Not all participants in the arm received all 5 different doses.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This Milestone represents 1 of the 5 different doses of the study. Dosing was variable and on an individual, per participant basis. All participants began treatment with the study drug at a dose of 1 mg/kg every other week. Dose escalations/reductions could be considered if the participant met protocol-defined criteria. Not all participants in the arm received all 5 different doses.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This Milestone represents 1 of the 5 different doses of the study. Dosing was variable and on an individual, per participant basis. All participants began treatment with the study drug at a dose of 1 mg/kg every other week. Dose escalations/reductions could be considered if the participant met protocol-defined criteria. Not all participants in the arm received all 5 different doses.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This Milestone represents 1 of the 5 different doses of the study. Dosing was variable and on an individual, per participant basis. All participants began treatment with the study drug at a dose of 1 mg/kg every other week. Dose escalations/reductions could be considered if the participant met protocol-defined criteria. Not all participants in the arm received all 5 different doses.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This Milestone represents 1 of the 5 different doses of the study. Dosing was variable and on an individual, per participant basis. All participants began treatment with the study drug at a dose of 1 mg/kg every other week. Dose escalations/reductions could be considered if the participant met protocol-defined criteria. Not all participants in the arm received all 5 different doses.

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This Milestone represents 1 of the 5 different doses of the study. Dosing was variable and on an individual, per participant basis. All participants began treatment with the study drug at a dose of 1 mg/kg every other week. Dose escalations/reductions could be considered if the participant met protocol-defined criteria. Not all participants in the arm received all 5 different doses.

[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This Milestone represents 1 of the 5 different doses of the study. Dosing was variable and on an individual, per participant basis. All participants began treatment with the study drug at a dose of 1 mg/kg every other week. Dose escalations/reductions could be considered if the participant met protocol-defined criteria. Not all participants in the arm received all 5 different doses.

[8] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This Milestone represents 1 of the 5 different doses of the study. Dosing was variable and on an individual, per participant basis. All participants began treatment with the study drug at a dose of 1 mg/kg every other week. Dose escalations/reductions could be considered if the participant met protocol-defined criteria. Not all participants in the arm received all 5 different doses.

[9] - The number of subjects at this milestone seems inconsistent with the number of subjects in the

arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This Milestone represents 1 of the 5 different doses of the study. Dosing was variable and on an individual, per participant basis. All participants began treatment with the study drug at a dose of 1 mg/kg every other week. Dose escalations/reductions could be considered if the participant met protocol-defined criteria. Not all participants in the arm received all 5 different doses.
[10] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This Milestone represents 1 of the 5 different doses of the study. Dosing was variable and on an individual, per participant basis. All participants began treatment with the study drug at a dose of 1 mg/kg every other week. Dose escalations/reductions could be considered if the participant met protocol-defined criteria. Not all participants in the arm received all 5 different doses.
[11] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This Milestone represents 1 of the 5 different doses of the study. Dosing was variable and on an individual, per participant basis. All participants began treatment with the study drug at a dose of 1 mg/kg every other week. Dose escalations/reductions could be considered if the participant met protocol-defined criteria. Not all participants in the arm received all 5 different doses.
[12] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This Milestone represents 1 of the 5 different doses of the study. Dosing was variable and on an individual, per participant basis. All participants began treatment with the study drug at a dose of 1 mg/kg every other week. Dose escalations/reductions could be considered if the participant met protocol-defined criteria. Not all participants in the arm received all 5 different doses.

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description:

Pediatric and adult participants initiated IV treatment with sebelipase alfa at a dose of 1 mg/kg qow. Participants were considered for a dose adjustment at the discretion of the Investigator and in consultation with the Sponsor. Dose escalation to 3 mg/kg qow was considered if pre-defined dose-escalation criteria were met. If these criteria continued to be met, a subsequent dose escalation to 3 mg/kg qw was considered. Dose decreases as low as 0.35 mg/kg qow were permitted based upon evidence of intolerance to sebelipase alfa treatment. Participants who completed the 96-week treatment period were permitted to continue receiving sebelipase alfa in an expanded treatment period for up to 48 weeks, pending local drug availability and study participation status.

Reporting group values	Overall Trial	Total	
Number of subjects	31	31	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	16	16	
Adolescents (12-17 years)	6	6	
Adults (18-64 years)	9	9	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	16.92		
standard deviation	± 14.678	-	
Gender categorical Units: Subjects			
Female	12	12	
Male	19	19	
Ethnicity Units: Subjects			
Hispanic or Latino	6	6	
Not Hispanic or Latino	25	25	
Race Units: Subjects			
White	27	27	
Other	4	4	

End points reporting groups

Reporting group title	2-<4 Years

Reporting group description:

This subgroup is part of the full analysis set and includes only participants between the ages of 2 and 4 years old who initiated intravenous (IV) treatment with sebelipase alfa at a dose of 1 milligram/kilogram (mg/kg) every other week (qow). Participants were considered for a dose adjustment at the discretion of the Investigator and in consultation with the Sponsor. Dose escalation to 3 mg/kg qow was considered if pre-defined dose-escalation criteria were met. If these criteria continued to be met, a subsequent dose escalation to 3 mg/kg every week (qw) was considered. Dose decreases as low as 0.35 mg/kg qow were permitted based upon evidence of intolerance to sebelipase alfa treatment. Participants who completed the 96-week treatment period were permitted to continue receiving sebelipase alfa in an expanded treatment period for up to 48 weeks, pending local drug availability and study participation status.

Reporting group title	4-18 Years

Reporting group description:

This subgroup is part of the full analysis set and includes only participants between the ages of 4 and 18 years old who initiated IV treatment with sebelipase alfa at a dose of 1 mg/kg qow. Participants were considered for a dose adjustment at the discretion of the Investigator and in consultation with the Sponsor. Dose escalation to 3 mg/kg qow was considered if pre-defined dose-escalation criteria were met. If these criteria continued to be met, a subsequent dose escalation to 3 mg/kg qw was considered. Dose decreases as low as 0.35 mg/kg qow were permitted based upon evidence of intolerance to sebelipase alfa treatment. Participants who completed the 96-week treatment period were permitted to continue receiving sebelipase alfa in an expanded treatment period for up to 48 weeks, pending local drug availability and study participation status.

Reporting group title	>18 Years

Reporting group description:

This subgroup is part of the full analysis set and includes only participants greater than 18 years old who initiated IV treatment with sebelipase alfa at a dose of 1 mg/kg qow. Participants were considered for a dose adjustment at the discretion of the Investigator and in consultation with the Sponsor. Dose escalation to 3 mg/kg qow was considered if pre-defined dose-escalation criteria were met. If these criteria continued to be met, a subsequent dose escalation to 3 mg/kg qw was considered. Dose decreases as low as 0.35 mg/kg qow were permitted based upon evidence of intolerance to sebelipase alfa treatment. Participants who completed the 96-week treatment period were permitted to continue receiving sebelipase alfa in an expanded treatment period for up to 48 weeks, pending local drug availability and study participation status.

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

All participants who received at least 1 infusion of sebelipase alfa. The full analysis set was used for analysis of safety and efficacy.

Subject analysis set title	Pediatric Participants
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This sub-group is part of the full analysis set and includes only those participants 18 years old or younger.

Primary: Participants Experiencing Severe Treatment-emergent Adverse Events (TEAEs)

End point title	Participants Experiencing Severe Treatment-emergent Adverse Events (TEAEs)[1]

End point description:

The number of participants experiencing severe TEAEs is presented for each age group who received sebelipase alfa in this open-label study. Information on AEs was obtained at each scheduled contact with the participant (or participant's parent or legal guardian), by specific questioning and, as appropriate, by examination. An AE was defined as any untoward medical occurrence in a participant that did not necessarily have to have a causal relationship with the administration of the study drug. An AE therefore could have been any unfavorable and unintended sign, symptom or disease temporally associated with the use of the study drug, whether or not considered related to the medicinal product. Pre-existing

conditions that worsened in severity during the course of the study were reported as AEs. AEs were recorded from the date of informed consent until completion of the follow-up phone call at 4 weeks after the last infusion of sebelipase alfa administered.

End point type	Primary

End point timeframe:

Week 144

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: Quantitative statistical analyses were not conducted on any of the reported safety data.

End point values	2-<4 Years	4-18 Years	>18 Years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	16	9	
Units: Participants	1	1	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change In Serum Lipids From Baseline To Week 144

End point title	Percent Change In Serum Lipids From Baseline To Week 144

End point description:

The effect of sebelipase alfa on lipid metabolism was evaluated by measuring the change from baseline to Week 144 in 4 serum lipids: low-density lipoprotein cholesterol (LDL-C); high-density lipoprotein cholesterol (HDL-C); non-HDL-C; triglycerides. Blood samples for these clinical laboratory tests were collected at scheduled time points and analyzed by a central laboratory.

End point type	Secondary

End point timeframe:

Baseline, Week 144

End point values	2-<4 Years	4-18 Years	>18 Years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5[2]	12[3]	2[4]	
Units: Percent Change				
median (full range (min-max))				
LDL-C	-37.5 (-52 to 25)	-29.2 (-59 to 23)	-22.5 (-37 to -8)	
HDL-C	76.5 (30 to 132)	24.2 (-4 to 90)	6.1 (-10 to 22)	
Non-HDL-C	-39.1 (-53 to 29)	-26.7 (-62 to 19)	-22.1 (-33 to -11)	
Triglycerides	-48.3 (-61 to 11)	-15.8 (-74 to 112)	-22.0 (-25 to -19)	

Notes:

[2] - N=5 for all 4 measurements

[3] - N=12 for all 4 measurements

[4] - N=2 for all 4 measurements

Statistical analyses

No statistical analyses for this end point

Secondary: Participants Testing Positive For Anti-drug Antibodies (ADAs)

End point title	Participants Testing Positive For Anti-drug Antibodies (ADAs)

End point description:

The impact of ADAs on the safety and immunogenicity of sebelipase alfa was evaluated by testing for ADAs in participants who received sebelipase alfa in this open-label study. Blood samples for assessment were collected prior to study infusions at Week 2, Week 4, Week 8, Week 12, and every 12 weeks thereafter. Participants testing positive for ADAs were also tested for the presence of neutralizing antibodies that inhibited sebelipase alfa enzyme activity and/or cellular uptake. Any participant experiencing a moderate or severe infusion-associated reaction (IAR) was to have an additional assessment of ADAs at the next study visit (prior to study drug infusion); these participants were to also have serum samples collected at 1 to 2 hours after IAR onset and at the next study visit (prior to study drug infusion) for analysis of serum tryptase. The number of participants who became ADA positive and who tested positive for neutralizing antibodies are presented.

End point type	Secondary

End point timeframe:

Week 144

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	31[5]			
Units: Participants				
ADA Positive	2			
Neutralizing Antibodies Positive	0			

Notes:

[5] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change In Body Mass Index (BMI)-For-Age Percentile From Baseline To Week 144 in Pediatric Participants

End point title	Percent Change In Body Mass Index (BMI)-For-Age Percentile From Baseline To Week 144 in Pediatric Participants

End point description:

To evaluate the effects of sebelipase alfa on growth parameters in pediatric participants (≤18 years old) presenting with evidence of growth delay, the percent change in the anthropometric parameter of BMI-for-age percentile from Baseline to Week 144 is reported. Anthropometric parameters were plotted on standard growth curves. When possible, historical data on growth parameters was also incorporated into the analyses. Percentiles and Z-scores for BMI-for-age were determined using standard growth charts appropriate to a participant's age on the date of the assessment: the World Health Organization standard growth chart for participants ≤2 years of age and the Centers for Disease Control standard growth chart for participants >2 years of age.

End point type	Secondary

End point timeframe:

Baseline, Week 144

End point values	Pediatric Participants			
Subject group type	Subject analysis set			
Number of subjects analysed	17[6]			
Units: Percent Change				
arithmetic mean (standard deviation)	26.45 (± 118.432)			

Notes:

[6] - Pediatric Participants (≤18 years old)

Statistical analyses

No statistical analyses for this end point

Secondary: Shift In Child-Pugh Status From Baseline To Week 144

End point title	Shift In Child-Pugh Status From Baseline To Week 144

End point description:

In order to evaluate the effects of sebelipase alfa on liver function, the number of participants with a shift in Child-Pugh status from Baseline to Week 144 is reported. The status is based on the Child-Pugh score, which is used in clinical practice to assess prognosis in individuals with chronic liver disease. Laboratory data were used in derivation of the score by summing individual scores (scored 1–3, with 3 indicating most severe) from clinical laboratory test results and physical examinations, including total serum bilirubin, serum albumin, prothrombin time, ascites, and hepatic encephalopathy. The total score was used to determine the Child-Pugh status, reported as Class A (score of 5 or 6), Class B (score of 7 to 9), or Class C (score of 10 to 15). Higher scores and higher categories represented a worse outcome. Data reported as 1 of 2 types of shifts in class: No Change from Baseline; Decline from Baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 144

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: Participants				
No Change: A to A	16			
No Change: B to B	1			
Decline: A to B	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Screening (up to 45 days prior to start of treatment) to Week 144.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups	
Reporting group title	0.35 mg/kg QOW
Reporting group description:	
This reporting group is based on the safety set and includes AEs with onset during the administration of IV treatment of sebelipase alfa at a dose of 0.35 mg/kg qow.	
Reporting group title	1.0 mg/kg QOW
Reporting group description:	
This reporting group is based on the safety set and includes AEs with onset during the administration of IV treatment of sebelipase alfa at a dose of 1.0 mg/kg qow.	
Reporting group title	1.0 mg/kg QW
Reporting group description:	
This reporting group is based on the safety set and includes AEs with onset during the administration of IV treatment of sebelipase alfa at a dose of 1.0 mg/kg qw.	
Reporting group title	3.0 mg/kg QOW
Reporting group description:	
This reporting group is based on the safety set and includes AEs with onset during the administration of IV treatment of sebelipase alfa at a dose of 3.0 mg/kg qow.	
Reporting group title	3.0 mg/kg QW
Reporting group description:	
This reporting group is based on the safety set and includes AEs with onset during the administration of IV treatment of sebelipase alfa at a dose of 3.0 mg/kg qw.	

Serious adverse events	0.35 mg/kg QOW	1.0 mg/kg QOW	1.0 mg/kg QW
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	8 / 31 (25.81%)	0 / 2 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	0 / 1 (0.00%)	1 / 31 (3.23%)	0 / 2 (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
Radius fracture			

subjects affected / exposed	0 / 1 (0.00%)	1 / 31 (3.23%)	0 / 2 (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
Vascular disorders			
Shock			
subjects affected / exposed	0 / 1 (0.00%)	1 / 31 (3.23%)	0 / 2 (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
Surgical and medical procedures			
Liver transplant			
subjects affected / exposed	0 / 1 (0.00%)	0 / 31 (0.00%)	0 / 2 (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			
Anaphylactic reaction			
subjects affected / exposed	0 / 1 (0.00%)	1 / 31 (3.23%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 1 (0.00%)	3 / 31 (9.68%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain lower			
subjects affected / exposed	0 / 1 (0.00%)	0 / 31 (0.00%)	0 / 2 (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 haemorrhage			
subjects affected / exposed	0 / 1 (0.00%)	1 / 31 (3.23%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic function abnormal			

subjects affected / exposed	0 / 1 (0.00%)	1 / 31 (3.23%)	0 / 2 (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
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	0 / 1 (0.00%)	1 / 31 (3.23%)	0 / 2 (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
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 31 (3.23%)	0 / 2 (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
Product issues			
Device breakage			
subjects affected / exposed	0 / 1 (0.00%)	1 / 31 (3.23%)	0 / 2 (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
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	0 / 1 (0.00%)	1 / 31 (3.23%)	0 / 2 (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

Serious adverse events	3.0 mg/kg QOW	3.0 mg/kg QW	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 11 (27.27%)	0 / 4 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	0 / 11 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			

subjects affected / exposed	0 / 11 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Shock			
subjects affected / exposed	0 / 11 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Liver transplant			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 11 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic function abnormal			

subjects affected / exposed	0 / 11 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	0 / 11 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device breakage			
subjects affected / exposed	0 / 11 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	0 / 11 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	0.35 mg/kg QOW	1.0 mg/kg QOW	1.0 mg/kg QW
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	30 / 31 (96.77%)	0 / 2 (0.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 1 (0.00%)	1 / 31 (3.23%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Vascular disorders			

Haematoma			
subjects affected / exposed	0 / 1 (0.00%)	1 / 31 (3.23%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Hypotension			
subjects affected / exposed	0 / 1 (0.00%)	1 / 31 (3.23%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Orthostatic hypotension			
subjects affected / exposed	0 / 1 (0.00%)	0 / 31 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 1 (0.00%)	15 / 31 (48.39%)	0 / 2 (0.00%)
occurrences (all)	0	26	0
Fatigue			
subjects affected / exposed	0 / 1 (0.00%)	2 / 31 (6.45%)	0 / 2 (0.00%)
occurrences (all)	0	3	0
Vaccination site erythema			
subjects affected / exposed	0 / 1 (0.00%)	0 / 31 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	0 / 1 (0.00%)	2 / 31 (6.45%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Reproductive system and breast disorders			
Balanoposthitis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 31 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 1 (0.00%)	7 / 31 (22.58%)	0 / 2 (0.00%)
occurrences (all)	0	13	0
Epistaxis			
subjects affected / exposed	0 / 1 (0.00%)	5 / 31 (16.13%)	0 / 2 (0.00%)
occurrences (all)	0	21	0
Oropharyngeal pain			

subjects affected / exposed	0 / 1 (0.00%)	3 / 31 (9.68%)	0 / 2 (0.00%)
occurrences (all)	0	3	0
Catarrh			
subjects affected / exposed	0 / 1 (0.00%)	2 / 31 (6.45%)	0 / 2 (0.00%)
occurrences (all)	0	6	0
Rhinorrhoea			
subjects affected / exposed	0 / 1 (0.00%)	3 / 31 (9.68%)	0 / 2 (0.00%)
occurrences (all)	0	8	0
Bronchospasm			
subjects affected / exposed	0 / 1 (0.00%)	2 / 31 (6.45%)	0 / 2 (0.00%)
occurrences (all)	0	3	0
Dyspnoea			
subjects affected / exposed	0 / 1 (0.00%)	1 / 31 (3.23%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Rhinitis allergic			
subjects affected / exposed	0 / 1 (0.00%)	2 / 31 (6.45%)	0 / 2 (0.00%)
occurrences (all)	0	6	0
Dysphonia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 31 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Tonsillar hypertrophy			
subjects affected / exposed	0 / 1 (0.00%)	0 / 31 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Investigations			
Body temperature increased			
subjects affected / exposed	0 / 1 (0.00%)	3 / 31 (9.68%)	0 / 2 (0.00%)
occurrences (all)	0	4	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 1 (0.00%)	2 / 31 (6.45%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 1 (0.00%)	0 / 31 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Alanine aminotransferase increased			

subjects affected / exposed	0 / 1 (0.00%)	1 / 31 (3.23%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 31 (3.23%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 31 (3.23%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Blood cholesterol increased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 31 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 31 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Low density lipoprotein increased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 31 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Protein total decreased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 31 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 1 (0.00%)	4 / 31 (12.90%)	0 / 2 (0.00%)
occurrences (all)	0	6	0
Limb injury			
subjects affected / exposed	0 / 1 (0.00%)	2 / 31 (6.45%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Bone contusion			
subjects affected / exposed	0 / 1 (0.00%)	1 / 31 (3.23%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Face injury			
subjects affected / exposed	0 / 1 (0.00%)	2 / 31 (6.45%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Arthropod bite			

subjects affected / exposed	0 / 1 (0.00%)	0 / 31 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Concussion			
subjects affected / exposed	0 / 1 (0.00%)	0 / 31 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Forearm fracture			
subjects affected / exposed	0 / 1 (0.00%)	0 / 31 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Procedural pain			
subjects affected / exposed	0 / 1 (0.00%)	0 / 31 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Scratch			
subjects affected / exposed	0 / 1 (0.00%)	0 / 31 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Skin abrasion			
subjects affected / exposed	0 / 1 (0.00%)	0 / 31 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Wound			
subjects affected / exposed	0 / 1 (0.00%)	0 / 31 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Left ventricular dilatation			
subjects affected / exposed	0 / 1 (0.00%)	0 / 31 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Left ventricular hypertrophy			
subjects affected / exposed	0 / 1 (0.00%)	0 / 31 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 1 (0.00%)	10 / 31 (32.26%)	0 / 2 (0.00%)
occurrences (all)	0	27	0
Dizziness			
subjects affected / exposed	0 / 1 (0.00%)	3 / 31 (9.68%)	0 / 2 (0.00%)
occurrences (all)	0	3	0
Hypoaesthesia			

subjects affected / exposed	0 / 1 (0.00%)	0 / 31 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	0 / 1 (0.00%)	1 / 31 (3.23%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 31 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Macrocytosis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 31 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 1 (0.00%)	12 / 31 (38.71%)	0 / 2 (0.00%)
occurrences (all)	0	23	0
Abdominal pain			
subjects affected / exposed	0 / 1 (0.00%)	11 / 31 (35.48%)	0 / 2 (0.00%)
occurrences (all)	0	17	0
Vomiting			
subjects affected / exposed	0 / 1 (0.00%)	9 / 31 (29.03%)	0 / 2 (0.00%)
occurrences (all)	0	20	0
Abdominal pain upper			
subjects affected / exposed	0 / 1 (0.00%)	5 / 31 (16.13%)	0 / 2 (0.00%)
occurrences (all)	0	7	0
Constipation			
subjects affected / exposed	0 / 1 (0.00%)	3 / 31 (9.68%)	0 / 2 (0.00%)
occurrences (all)	0	5	0
Nausea			
subjects affected / exposed	0 / 1 (0.00%)	3 / 31 (9.68%)	0 / 2 (0.00%)
occurrences (all)	0	3	0
Dental caries			
subjects affected / exposed	0 / 1 (0.00%)	2 / 31 (6.45%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Gastritis			

subjects affected / exposed	0 / 1 (0.00%)	1 / 31 (3.23%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Gingival bleeding			
subjects affected / exposed	0 / 1 (0.00%)	2 / 31 (6.45%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Toothache			
subjects affected / exposed	0 / 1 (0.00%)	2 / 31 (6.45%)	0 / 2 (0.00%)
occurrences (all)	0	3	0
Oral contusion			
subjects affected / exposed	0 / 1 (0.00%)	0 / 31 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Tongue eruption			
subjects affected / exposed	0 / 1 (0.00%)	0 / 31 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 31 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	0 / 1 (0.00%)	4 / 31 (12.90%)	0 / 2 (0.00%)
occurrences (all)	0	20	0
Dermatitis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 31 (3.23%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Eczema			
subjects affected / exposed	0 / 1 (0.00%)	1 / 31 (3.23%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Erythema			
subjects affected / exposed	0 / 1 (0.00%)	1 / 31 (3.23%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Petechiae			
subjects affected / exposed	0 / 1 (0.00%)	2 / 31 (6.45%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Rash			

subjects affected / exposed	0 / 1 (0.00%)	2 / 31 (6.45%)	0 / 2 (0.00%)
occurrences (all)	0	4	0
Rash papular			
subjects affected / exposed	0 / 1 (0.00%)	1 / 31 (3.23%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Skin lesion			
subjects affected / exposed	0 / 1 (0.00%)	2 / 31 (6.45%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Urticaria			
subjects affected / exposed	0 / 1 (0.00%)	2 / 31 (6.45%)	0 / 2 (0.00%)
occurrences (all)	0	11	0
Dry skin			
subjects affected / exposed	0 / 1 (0.00%)	0 / 31 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	0 / 1 (0.00%)	2 / 31 (6.45%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Endocrine disorders			
Delayed puberty			
subjects affected / exposed	0 / 1 (0.00%)	0 / 31 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 1 (0.00%)	2 / 31 (6.45%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Back pain			
subjects affected / exposed	0 / 1 (0.00%)	2 / 31 (6.45%)	0 / 2 (0.00%)
occurrences (all)	0	3	0
Musculoskeletal pain			
subjects affected / exposed	0 / 1 (0.00%)	2 / 31 (6.45%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 1 (0.00%)	13 / 31 (41.94%)	0 / 2 (0.00%)
occurrences (all)	0	29	0

Upper respiratory tract infection			
subjects affected / exposed	0 / 1 (0.00%)	7 / 31 (22.58%)	0 / 2 (0.00%)
occurrences (all)	0	8	0
Gastroenteritis			
subjects affected / exposed	0 / 1 (0.00%)	6 / 31 (19.35%)	0 / 2 (0.00%)
occurrences (all)	0	9	0
Pharyngitis			
subjects affected / exposed	0 / 1 (0.00%)	6 / 31 (19.35%)	0 / 2 (0.00%)
occurrences (all)	0	8	0
Respiratory tract infection			
subjects affected / exposed	0 / 1 (0.00%)	7 / 31 (22.58%)	0 / 2 (0.00%)
occurrences (all)	0	14	0
Conjunctivitis			
subjects affected / exposed	0 / 1 (0.00%)	2 / 31 (6.45%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Bronchitis			
subjects affected / exposed	0 / 1 (0.00%)	3 / 31 (9.68%)	0 / 2 (0.00%)
occurrences (all)	0	4	0
Ear infection			
subjects affected / exposed	0 / 1 (0.00%)	3 / 31 (9.68%)	0 / 2 (0.00%)
occurrences (all)	0	3	0
Eye infection			
subjects affected / exposed	0 / 1 (0.00%)	2 / 31 (6.45%)	0 / 2 (0.00%)
occurrences (all)	0	3	0
Influenza			
subjects affected / exposed	0 / 1 (0.00%)	3 / 31 (9.68%)	0 / 2 (0.00%)
occurrences (all)	0	5	0
Oral herpes			
subjects affected / exposed	0 / 1 (0.00%)	1 / 31 (3.23%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Otitis media acute			
subjects affected / exposed	0 / 1 (0.00%)	3 / 31 (9.68%)	0 / 2 (0.00%)
occurrences (all)	0	3	0
Rhinitis			
subjects affected / exposed	0 / 1 (0.00%)	3 / 31 (9.68%)	0 / 2 (0.00%)
occurrences (all)	0	5	0

Sinusitis			
subjects affected / exposed	0 / 1 (0.00%)	3 / 31 (9.68%)	0 / 2 (0.00%)
occurrences (all)	0	4	0
Urinary tract infection			
subjects affected / exposed	0 / 1 (0.00%)	2 / 31 (6.45%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Acute sinusitis			
subjects affected / exposed	0 / 1 (0.00%)	2 / 31 (6.45%)	0 / 2 (0.00%)
occurrences (all)	0	4	0
Gastroenteritis viral			
subjects affected / exposed	0 / 1 (0.00%)	1 / 31 (3.23%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Hordeolum			
subjects affected / exposed	0 / 1 (0.00%)	2 / 31 (6.45%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Pharyngotonsillitis			
subjects affected / exposed	0 / 1 (0.00%)	2 / 31 (6.45%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 1 (0.00%)	1 / 31 (3.23%)	0 / 2 (0.00%)
occurrences (all)	0	4	0
Tonsillitis			
subjects affected / exposed	0 / 1 (0.00%)	2 / 31 (6.45%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Viral infection			
subjects affected / exposed	0 / 1 (0.00%)	2 / 31 (6.45%)	0 / 2 (0.00%)
occurrences (all)	0	3	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 1 (0.00%)	1 / 31 (3.23%)	0 / 2 (0.00%)
occurrences (all)	0	3	0
Gastritis viral			
subjects affected / exposed	0 / 1 (0.00%)	0 / 31 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Molluscum contagiosum			
subjects affected / exposed	0 / 1 (0.00%)	0 / 31 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0

Tracheitis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 31 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Varicella zoster virus infection			
subjects affected / exposed	0 / 1 (0.00%)	0 / 31 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Vitamin D deficiency			
subjects affected / exposed	0 / 1 (0.00%)	4 / 31 (12.90%)	0 / 2 (0.00%)
occurrences (all)	0	5	0
Iron deficiency			
subjects affected / exposed	0 / 1 (0.00%)	2 / 31 (6.45%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Hypomagnesaemia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 31 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	3.0 mg/kg QOW	3.0 mg/kg QW	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 11 (90.91%)	4 / 4 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Vascular disorders			
Haematoma			
subjects affected / exposed	2 / 11 (18.18%)	0 / 4 (0.00%)	
occurrences (all)	5	0	
Hypotension			
subjects affected / exposed	0 / 11 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Orthostatic hypotension			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	4 / 11 (36.36%)	1 / 4 (25.00%)	
occurrences (all)	4	1	
Fatigue			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Vaccination site erythema			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	0 / 11 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Reproductive system and breast disorders			
Balanoposthitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 11 (9.09%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
Epistaxis			
subjects affected / exposed	3 / 11 (27.27%)	1 / 4 (25.00%)	
occurrences (all)	13	1	
Oropharyngeal pain			
subjects affected / exposed	1 / 11 (9.09%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
Catarrh			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
subjects affected / exposed	0 / 11 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Bronchospasm			
subjects affected / exposed	0 / 11 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	

Dyspnoea			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Rhinitis allergic			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Dysphonia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Tonsillar hypertrophy			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Investigations			
Body temperature increased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 11 (9.09%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 11 (9.09%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 11 (9.09%)	1 / 4 (25.00%)	
occurrences (all)	1	2	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Blood cholesterol increased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
C-reactive protein increased			

subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Low density lipoprotein increased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Protein total decreased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	3 / 11 (27.27%)	0 / 4 (0.00%)	
occurrences (all)	6	0	
Limb injury			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Bone contusion			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Face injury			
subjects affected / exposed	0 / 11 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Arthropod bite			
subjects affected / exposed	0 / 11 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	3	
Concussion			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Forearm fracture			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Procedural pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	2	
Scratch			

subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Skin abrasion			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Wound			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Left ventricular dilatation			
subjects affected / exposed	0 / 11 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Left ventricular hypertrophy			
subjects affected / exposed	0 / 11 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 11 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Dizziness			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Hypoaesthesia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Migraine			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Macrocytosis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			

Diarrhoea				
subjects affected / exposed	2 / 11 (18.18%)	1 / 4 (25.00%)		
occurrences (all)	4	1		
Abdominal pain				
subjects affected / exposed	2 / 11 (18.18%)	0 / 4 (0.00%)		
occurrences (all)	2	0		
Vomiting				
subjects affected / exposed	2 / 11 (18.18%)	1 / 4 (25.00%)		
occurrences (all)	2	1		
Abdominal pain upper				
subjects affected / exposed	2 / 11 (18.18%)	0 / 4 (0.00%)		
occurrences (all)	3	0		
Constipation				
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)		
occurrences (all)	1	0		
Nausea				
subjects affected / exposed	2 / 11 (18.18%)	1 / 4 (25.00%)		
occurrences (all)	4	1		
Dental caries				
subjects affected / exposed	0 / 11 (0.00%)	0 / 4 (0.00%)		
occurrences (all)	0	0		
Gastritis				
subjects affected / exposed	2 / 11 (18.18%)	0 / 4 (0.00%)		
occurrences (all)	2	0		
Gingival bleeding				
subjects affected / exposed	0 / 11 (0.00%)	0 / 4 (0.00%)		
occurrences (all)	0	0		
Toothache				
subjects affected / exposed	0 / 11 (0.00%)	0 / 4 (0.00%)		
occurrences (all)	0	0		
Oral contusion				
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)		
occurrences (all)	1	0		
Tongue eruption				
subjects affected / exposed	0 / 11 (0.00%)	1 / 4 (25.00%)		
occurrences (all)	0	1		

Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	2 / 11 (18.18%)	0 / 4 (0.00%)	
occurrences (all)	10	0	
Dermatitis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Eczema			
subjects affected / exposed	1 / 11 (9.09%)	1 / 4 (25.00%)	
occurrences (all)	4	3	
Erythema			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Petechiae			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	1 / 11 (9.09%)	1 / 4 (25.00%)	
occurrences (all)	4	1	
Rash papular			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Skin lesion			
subjects affected / exposed	0 / 11 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Urticaria			
subjects affected / exposed	0 / 11 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Dry skin			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			

Urinary incontinence			
subjects affected / exposed	0 / 11 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Endocrine disorders			
Delayed puberty			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Back pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 11 (36.36%)	3 / 4 (75.00%)	
occurrences (all)	6	4	
Upper respiratory tract infection			
subjects affected / exposed	2 / 11 (18.18%)	2 / 4 (50.00%)	
occurrences (all)	2	3	
Gastroenteritis			
subjects affected / exposed	1 / 11 (9.09%)	2 / 4 (50.00%)	
occurrences (all)	1	2	
Pharyngitis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection			
subjects affected / exposed	1 / 11 (9.09%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
Conjunctivitis			
subjects affected / exposed	1 / 11 (9.09%)	1 / 4 (25.00%)	
occurrences (all)	1	1	

Bronchitis				
subjects affected / exposed	0 / 11 (0.00%)	0 / 4 (0.00%)		
occurrences (all)	0	0		
Ear infection				
subjects affected / exposed	0 / 11 (0.00%)	0 / 4 (0.00%)		
occurrences (all)	0	0		
Eye infection				
subjects affected / exposed	1 / 11 (9.09%)	1 / 4 (25.00%)		
occurrences (all)	1	1		
Influenza				
subjects affected / exposed	0 / 11 (0.00%)	0 / 4 (0.00%)		
occurrences (all)	0	0		
Oral herpes				
subjects affected / exposed	2 / 11 (18.18%)	0 / 4 (0.00%)		
occurrences (all)	2	0		
Otitis media acute				
subjects affected / exposed	0 / 11 (0.00%)	0 / 4 (0.00%)		
occurrences (all)	0	0		
Rhinitis				
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)		
occurrences (all)	6	0		
Sinusitis				
subjects affected / exposed	0 / 11 (0.00%)	0 / 4 (0.00%)		
occurrences (all)	0	0		
Urinary tract infection				
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)		
occurrences (all)	1	0		
Acute sinusitis				
subjects affected / exposed	0 / 11 (0.00%)	0 / 4 (0.00%)		
occurrences (all)	0	0		
Gastroenteritis viral				
subjects affected / exposed	1 / 11 (9.09%)	1 / 4 (25.00%)		
occurrences (all)	2	3		
Hordeolum				
subjects affected / exposed	0 / 11 (0.00%)	0 / 4 (0.00%)		
occurrences (all)	0	0		

Pharyngotonsillitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Respiratory tract infection viral			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Tonsillitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Viral infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Gastritis viral			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Molluscum contagiosum			
subjects affected / exposed	0 / 11 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Tracheitis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Varicella zoster virus infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Vitamin D deficiency			
subjects affected / exposed	2 / 11 (18.18%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Iron deficiency			
subjects affected / exposed	0 / 11 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Hypomagnesaemia			

subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 4 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 February 2015	– Removed 'seroconversion rate' and 'time to seroconversion' from the immunogenicity outcome variables. The intent was to characterize ADAs for all isotypes. In this study, a participant was considered to be ADA positive if they had at least 1 positive ADA titer at any time during the study. However, a single positive ADA result would not necessarily imply that a participant had seroconverted. Moreover, analysis of tolerization (for which no standard definition exists) would not be appropriate to these circumstances. – Limited liver biopsy by the transjugular method to participants with advanced liver disease (as local facilities permitted), rather than recommending this for all study participants. – Updated the guidance on the management of IARs based on clinical experience in other ongoing studies with sebelipase alfa. – Clarified that AEs collected during hospitalization would be assessed and reported. – Clarified that AEs occurring after signing the informed consent but before the first dose of study drug would only be recorded if deemed related to study procedures or requirements.
07 December 2015	- Clarified that the minimum duration of treatment would be "at least 52 weeks." This clarification was added in response to Pediatric Committee comments on the paediatric investigation plan request for modification. - Added a pharmacokinetics (PK) profile for participants receiving a dose decrease (the protocol already required a PK profile for participants receiving a dose increase), and added an ADA assessment prior to the first infusion at the new dose for all participants receiving a dose modification (increase or decrease). These additional data will support an evaluation of the relationship between immunogenicity, sebelipase alfa exposure, and clinical response during long-term treatment with sebelipase alfa.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported