Clinical trial results:
An Open Label Multicenter Extension Study to Evaluate the Long-Term Safety, Tolerability, and Efficacy of SBC-102 in Adult Subjects with Liver Dysfunction Due to Lysosomal Acid Lipase Deficiency Who Previously Received Treatment in Study LAL-CL01

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2011-001513-13
Trial protocol	GB CZ
Global end of trial date	21 June 2017

Results information

Result version number	v1
This version publication date	08 July 2018
First version publication date	08 July 2018

Trial information

Trial identification

Sponsor protocol code	LAL-CL04

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01488097
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alexion Pharmaceuticals
Sponsor organisation address	100 College Street, New Haven, CT, United States, 06510
Public contact	Alexion Pharmaceuticals, Alexion Pharmaceuticals, 001 7814302497, clinicaltrials@alexion.com
Scientific contact	Alexion Pharmaceuticals, Alexion Pharmaceuticals, 001 7814302497, clinicaltrials@alexion.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 June 2017
Global end of trial reached?	Yes
Global end of trial date	21 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the long-term safety and tolerability of sebelipase alfa in participants with liver dysfunction due to Lysosomal Acid Lipase (LAL) Deficiency.

Protection of trial subjects:

This study was conducted according to applicable Good Clinical Practice regulations and International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines, as well as relevant institutional research policies and procedures and according to ethical principles that have their origin in the Declaration of Helsinki.

All participants in this study were provided a consent form describing the study and providing sufficient information for participants to make an informed decision about their participation in the study. This consent form was submitted with the protocol for review and approval by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) for the study. The formal consent of the participant, using the IRB/IEC-approved consent form, was obtained before that participant underwent any study procedure.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 December 2011
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	United Kingdom: 2
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	8
EEA total number of subjects	4

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	8
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants who successfully received all 4 doses of sebelipase alfa in Study LAL-CL01 and opted to continue treatment in the extension study underwent screening assessments to determine study eligibility. Eligible participants initiated treatment in the extension study at least 4 weeks after their last dose of sebelipase alfa in Study LAL-CL01.

Pre-assignment

Screening details:

9 participants who completed Study LAL-CL01 (received all 4 doses of sebelipase alfa) were screened for eligibility for enrollment in this extension study (LAL-CL04). 8 participants met all enrollment criteria and were enrolled. 1 participant who required a liver transplant no longer met the entry criteria.

Period 1

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

Blinding implementation details:

This is an open-label study.

Arms

Arm title	Open-Label Sebelipase Alfa

Arm description:

Participants were administered sebelipase alfa once weekly (qw) as an intravenous (IV) infusion at the same dose received in Study LAL-CL01 (0.35, 1, or 3 milligrams per kilogram [mg/kg]) for 4 weeks. After the initial 4 qw doses, participants transitioned to dosing every other week (qow) at either 1 mg/kg (participants who initiated treatment at 0.35 or 1 mg/kg qw) or 3 mg/kg (participants who initiated dosing at 3 mg/kg qw). Subsequent modifications to the dose and dosing frequency were permitted for individual participants based on observed safety, tolerability, and clinical response to treatment. Participants could continue to receive treatment with sebelipase alfa for up to 5 years.

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

Dosage and administration details:

IV infusions of sebelipase alfa at 0.35, 1, or 3 mg/kg administered qw for 4 weeks and IV infusions of sebelipase alfa at 1 or 3 mg/kg administered qow for up to 5 years.

Number of subjects in period 1	Open-Label Sebelipase Alfa
Started	8
Received Study Drug in Extension Study	8
Completed	7
Not completed	1
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial
Reporting group description:	
All participants who received any amount of study drug in the extension study.	

Reporting group values	Overall Trial	Total	
Number of subjects	8	8	
Age categorical Units: Subjects			
Adults (18-64 years)	8	8	
Age continuous Units: years			
arithmetic mean	30.3		
standard deviation	± 10.69	-	
Gender categorical Units: Subjects			
Female	2	2	
Male	6	6	
Race Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	8	8	
More than one race	0	0	
Unknown or Not Reported	0	0	
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	8	8	
Unknown or not reported	0	0	

End points

End points reporting groups

Reporting group title	Open-Label Sebelipase Alfa

Reporting group description:

Participants were administered sebelipase alfa once weekly (qw) as an intravenous (IV) infusion at the same dose received in Study LAL-CL01 (0.35, 1, or 3 milligrams per kilogram [mg/kg]) for 4 weeks. After the initial 4 qw doses, participants transitioned to dosing every other week (qow) at either 1 mg/kg (participants who initiated treatment at 0.35 or 1 mg/kg qw) or 3 mg/kg (participants who initiated dosing at 3 mg/kg qw). Subsequent modifications to the dose and dosing frequency were permitted for individual participants based on observed safety, tolerability, and clinical response to treatment. Participants could continue to receive treatment with sebelipase alfa for up to 5 years.

Subject analysis set title	Sebelipase Alfa 1 mg/kg
Subject analysis set type	Full analysis

Subject analysis set description:

Participants were administered sebelipase alfa qw as an IV infusion at the same dose received in Study LAL-CL01 (0.35, 1, or 3 mg/kg) for 4 weeks. After the initial 4 qw doses, participants transitioned to dosing qow at 1 mg/kg (participants who initiated treatment at 0.35 or 1 mg/kg qw). Subsequent modifications to the dose and dosing frequency were permitted for individual participants based on observed safety, tolerability, and clinical response to treatment. Participants could continue to receive treatment with sebelipase alfa for up to 5 years.

Subject analysis set title	Sebelipase Alfa 3 mg/kg
Subject analysis set type	Full analysis

Subject analysis set description:

Participants were administered sebelipase alfa qw as an IV infusion at the same dose received in Study LAL-CL01 (0.35, 1, or 3 mg/kg) for 4 weeks. After the initial 4 qw doses, participants transitioned to dosing qow at 3 mg/kg (participants who initiated dosing at 3 mg/kg qw). Subsequent modifications to the dose and dosing frequency were permitted for individual participants based on observed safety, tolerability, and clinical response to treatment. Participants could continue to receive treatment with sebelipase alfa for up to 5 years.

Primary: Number Of Participants Reporting TEAEs And IARs

End point title	Number Of Participants Reporting TEAEs And IARs[1]

End point description:

Safety and tolerability of sebelipase alfa was primarily assessed by monitoring the number of participants reporting treatment-emergent adverse events (TEAEs), including serious adverse events, and infusion-associated reactions (IARs). The number of participants who discontinued from the study due to a TEAE is also presented. An IAR was defined as any adverse event that occurred during the 2-hour (hr) infusion or within 4 hrs after the end of the infusion and was assessed by the investigator as at least possibly related to study drug. A summary of serious and all other non-serious adverse events regardless of causality is located in the Reported Adverse Events module. TEAEs that occurred after the first dose administration at Week 1 through the End of Study (EOS) are presented. End of study was 30 days (+ 7 days) after the last dose of study drug (at Week 260).

End point type	Primary

End point timeframe:

From after first dose administration post-Baseline through EOS during study LAL-CL04

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical hypothesis testing was planned for this primary endpoint.

End point values	Open-Label Sebelipase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: Count of Participants				
TEAEs	8			
Serious TEAEs	1			
IARs	2			
TEAEs Leading to Study Discontinuation	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Changes From Baseline In ALT And AST

End point title	Changes From Baseline In ALT And AST

End point description:

Changes from Baseline to Week 12, Week 24, Week 52, Week 104, Week 156, Week 208, Week 260, and EOS for alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Baseline values were defined as the last measurement prior to the first infusion of sebelipase alfa in Study LAL-CL04. The analysis population includes participants in the Full Analysis Set (FAS) for whom ALT and AST data were available at both Baseline and the indicated post-treatment time point. The FAS included all participants who received at least 1 complete infusion of sebelipase alfa in this study and who had at least 1 post-treatment measurement in this study.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 24, Week 52, Week 104, Week 156, Week 208, Week 260, and EOS

End point values	Open-Label Sebelipase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: units (U)/liter (L)				
arithmetic mean (standard deviation)				
ALT Week 12 (n=8)	-35.9 (± 19.99)			
ALT Week 24 (n=8)	-38.1 (± 24.00)			
ALT Week 52 (n=7)	-40.6 (± 20.50)			
ALT Week 104 (n=8)	-42.5 (± 19.65)			
ALT Week 156 (n=8)	-29.5 (± 20.38)			
ALT Week 208 (n=7)	-26.7 (± 30.58)			
ALT Week 260 (n=5)	-31.6 (± 21.78)			
ALT EOS (n=7)	-26.6 (± 31.10)			
AST Week 12 (n=8)	-13.9 (± 7.02)			

AST Week 24 (n=8)	-12.4 (± 11.71)			
AST Week 52 (n=7)	-18.6 (± 12.82)			
AST Week 104 (n=8)	-11.8 (± 15.59)			
AST Week 156 (n=8)	-12.8 (± 9.95)			
AST Week 208 (n=7)	-10.4 (± 14.86)			
AST Week 260 (n=5)	-10.8 (± 13.70)			
AST EOS (n=5)	-15.3 (± 14.27)			

Statistical analyses

No statistical analyses for this end point

Secondary: Changes From Baseline In Liver Volume

End point title	Changes From Baseline In Liver Volume

End point description:

Changes in liver volume from Baseline to Week 10 or 12, Week 24, Week 52, Week 104, Week 156, Week 208, Week 260, and EOS was assessed by magnetic resonance imaging (MRI). Baseline values were defined as the last measurement prior to the first infusion of sebelipase alfa in Study LAL-CL04. Liver volume was expressed as multiples of normal (MN), where normal is defined as 2.5% of body weight. The analysis population includes participants in the FAS for whom liver volume data were available at both Baseline and the indicated post-treatment time point. The FAS included all participants who received at least 1 complete infusion of sebelipase alfa in this study and who had at least 1 post-treatment measurement in this study.

End point type	Secondary

End point timeframe:

Baseline, Week 10 or 12, Week 24, Week 52, Week 104, Week 156, Week 208, Week 260, and EOS

End point values	Open-Label Sebelipase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: Multiples of Normal (MN)				
arithmetic mean (standard deviation)				
Week 10 or 12 (n=8)	-0.096 (± 0.0892)			
Week 24 (n=8)	-0.099 (± 0.1513)			
Week 52 (n=7)	-0.096 (± 0.0641)			
Week 104 (n=7)	-0.176 (± 0.0801)			
Week 156 (n=5)	-0.082 (± 0.0732)			
Week 208 (n=5)	-0.182 (± 0.0556)			
Week 260 (n=2)	-0.218 (± 0.0388)			

EOS (n=2)	-0.205 (± 0.0358)			

Statistical analyses

No statistical analyses for this end point

Secondary: Changes From Baseline In Liver Fat Content

End point title	Changes From Baseline In Liver Fat Content

End point description:

Changes in liver fat content from Baseline to Week 10 or 12, Week 24, Week 52, Week 104, Week 156, Week 208, and Week 260, as assessed by multi-echo gradient-echo MRI. Baseline values were defined as the last measurement prior to the first infusion of sebelipase alfa in Study LAL-CL04. The analysis population includes participants in the FAS for whom liver fat content data were available at both Baseline and the indicated post-treatment time point. The FAS included all participants who received at least 1 complete infusion of sebelipase alfa in this study and who had at least 1 post-treatment measurement in this study.

End point type	Secondary

End point timeframe:

Baseline, Week 10 or 12, Week 24, Week 52, Week 104, Week 156, Week 208, and Week 260

End point values	Open-Label Sebelipase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: Percentage fat fraction				
arithmetic mean (standard deviation)				
Week 10 or 12 (n=5)	-2.816 (± 1.8025)			
Week 24 (n=5)	-2.772 (± 3.0024)			
Week 52 (n=4)	-3.633 (± 2.5736)			
Week 104 (n=4)	-4.348 (± 2.4486)			
Week 156 (n=4)	-3.953 (± 4.1182)			
Week 208 (n=3)	-4.007 (± 3.4260)			
Week 260 (n=2)	-0.060 (± 3.4507)			

Statistical analyses

No statistical analyses for this end point

Secondary: Changes From Baseline In GGT And ALP

End point title	Changes From Baseline In GGT And ALP

End point description:

Changes from Baseline to Week 12, Week 24, Week 52, Week 104, Week 156, Week 208, Week 260, and EOS for gamma glutamyltransferase (GGT) and alkaline phosphatase (ALP). Baseline values were defined as the last measurement prior to the first infusion of sebelipase alfa in Study LAL-CL04. The analysis population includes participants in the FAS for whom GGT and ALP data were available at both Baseline and the indicated post-treatment time point. The FAS included all participants who received at least 1 complete infusion of sebelipase alfa in this study and who had at least 1 post-treatment measurement in this study.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 24, Week 52, Week 104, Week 156, Week 208, Week 260, and EOS

End point values	Open-Label Sebelipase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: U/L				
arithmetic mean (standard deviation)				
GGT Week 12 (n=8)	-13.6 (± 28.79)			
GGT Week 24 (n=8)	-13.8 (± 24.63)			
GGT Week 52 (n=7)	-14.0 (± 18.89)			
GGT Week 104 (n=8)	-22.4 (± 34.01)			
GGT Week 156 (n=8)	0.1 (± 11.32)			
GGT Week 208 (n=7)	2.3 (± 10.13)			
GGT Week 260 (n=5)	-6.0 (± 12.33)			
GGT EOS (n=7)	-4.0 (± 7.70)			
ALP Week 12 (n=8)	-15.3 (± 12.09)			
ALP Week 24 (n=8)	-18.3 (± 20.74)			
ALP Week 52 (n=7)	-12.4 (± 18.78)			
ALP Week 104 (n=8)	-18.0 (± 9.68)			
ALP Week 156 (n=8)	-6.4 (± 11.81)			
ALP Week 208 (n=7)	-5.9 (± 16.60)			
ALP Week 260 (n=5)	-14.2 (± 21.32)			
ALP EOS (n=7)	-7.9 (± 20.82)			

Statistical analyses

No statistical analyses for this end point

Secondary: Changes From Baseline In Serum Lipids

End point title	Changes From Baseline In Serum Lipids

End point description:

Lipid changes from Baseline to Week 10 or 12, Week 24, Week 52, Week 104, Week 156, Week 208, Week 260, and EOS were measured in serum for total cholesterol (Total-C), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), and triglycerides (TG). Baseline values were defined as the last measurement prior to the first infusion of sebelipase alfa in Study LAL-CL04. The analysis population includes participants in the FAS for whom lipid data were available at both Baseline and the indicated post-treatment time point. The FAS included all participants who received at least 1 complete infusion of sebelipase alfa in this study and who had at least 1 post-treatment measurement in this study.

End point type	Secondary

End point timeframe:

Baseline, Week 10 or 12, Week 24, Week 52, Week 104, Week 156, Week 208, Week 260, and EOS

End point values	Open-Label Sebelipase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: mg/dL				
arithmetic mean (standard deviation)				
Total-C Week 12 (n=8)	-34.5 (± 40.50)			
Total-C Week 24 (n=8)	-59.3 (± 38.83)			
Total-C Week 52 (n=7)	-73.9 (± 54.43)			
Total-C Week 104 (n=8)	-60.8 (± 50.82)			
Total-C Week 156 (n=8)	-36.4 (± 43.90)			
Total-C Week 208 (n=7)	1.1 (± 93.21)			
Total-C Week 260 (n=5)	-45.5 (± 50.85)			
Total-C EOS (n=7)	-21.9 (± 59.89)			
HDL-C Week 12 (n=8)	4.9 (± 3.95)			
HDL-C Week 24 (n=8)	5.7 (± 6.19)			
HDL-C Week 52 (n=7)	9.0 (± 7.25)			
HDL-C Week 104 (n=8)	6.5 (± 9.04)			
HDL-C Week 156 (n=8)	5.2 (± 9.50)			
HDL-C Week 208 (n=7)	4.9 (± 4.91)			
HDL-C Week 260 (n=5)	3.4 (± 8.96)			
HDL-C EOS (n=7)	6.7 (± 9.02)			
LDL-C Week 12 (n=8)	-34.1 (± 37.54)			
LDL-C Week 24 (n=8)	-68.5 (± 40.22)			
LDL-C Week 52 (n=7)	-78.5 (± 50.91)			
LDL-C Week 104 (n=8)	-68.7 (± 43.11)			
LDL-C Week 156 (n=8)	-40.8 (± 38.91)			
LDL-C Week 208 (n=7)	-20.5 (± 66.41)			
LDL-C Week 260 (n=5)	-43.4 (± 44.05)			

LDL-C EOS (n=7)	-35.0 (± 42.27)			
TG Week 12 (n=8)	-18.5 (± 71.93)			
TG Week 24 (n=8)	-17.5 (± 37.62)			
TG Week 52 (n=7)	-45.2 (± 66.91)			
TG Week 104 (n=8)	-24.0 (± 84.25)			
TG Week 156 (n=8)	-11.2 (± 60.45)			
TG Week 208 (n=7)	5.6 (± 94.18)			
TG Week 260 (n=5)	-4.8 (± 66.03)			
TG EOS (n=7)	15.7 (± 106.54)			

Statistical analyses

No statistical analyses for this end point

Secondary: Changes From Baseline In Serum Ferritin

End point title	Changes From Baseline In Serum Ferritin

End point description:

Changes from Baseline to Week 12, Week 24, Week 52, Week 104, Week 156, Week 208, Week 260, and EOS for serum ferritin. Baseline values were defined as the last measurement prior to the first infusion of sebelipase alfa in Study LAL-CL04. The analysis population includes participants in the FAS for whom serum ferritin data were available at both Baseline and the indicated post-treatment time point. The FAS included all participants who received at least 1 complete infusion of sebelipase alfa in this study and who had at least 1 post-treatment measurement in this study.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 24, Week 52, Week 104, Week 156, Week 208, Week 260, and EOS

End point values	Open-Label Sebelipase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: micrograms (µg)/L				
arithmetic mean (standard deviation)				
Week 12 (n=8)	-37.0 (± 29.93)			
Week 24 (n=8)	-40.1 (± 47.27)			
Week 52 (n=7)	-18.1 (± 32.68)			
Week 104 (n=8)	-22.8 (± 44.57)			
Week 156 (n=8)	0.0 (± 34.50)			
Week 208 (n=7)	18.0 (± 40.41)			
Week 260 (n=5)	63.0 (± 70.53)			
EOS (n=7)	47.7 (± 56.06)			

Statistical analyses

No statistical analyses for this end point

Secondary: Changes From Baseline In Hs-CRP

End point title	Changes From Baseline In Hs-CRP

End point description:

Changes from Baseline to Week 12, Week 24, Week 52, Week 104, Week 156, Week 208, Week 260, and EOS for High sensitivity C-reactive protein (hs-CRP). Baseline values were defined as the last measurement prior to the first infusion of sebelipase alfa in Study LAL-CL04. The analysis population includes participants in the FAS for whom hs-CRP data were available at both Baseline and the indicated post-treatment time point. The FAS included all participants who received at least 1 complete infusion of sebelipase alfa in this study and who had at least 1 post-treatment measurement in this study.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 24, Week 52, Week 104, Week 156, Week 208, Week 260, and EOS

End point values	Open-Label Sebelipase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: mg/L				
arithmetic mean (standard deviation)				
Week 12 (n=8)	-1.41 (± 3.022)			
Week 24 (n=8)	-1.03 (± 3.945)			
Week 52 (n=7)	-1.40 (± 3.245)			
Week 104 (n=8)	-1.50 (± 4.079)			
Week 156 (n=8)	-1.09 (± 3.323)			
Week 208 (n=7)	-1.34 (± 3.674)			
Week 260 (n=5)	-0.16 (± 0.619)			
EOS (n=7)	-1.33 (± 2.985)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From after first dose administration post-Baseline through EOS during study LAL-CL04

Adverse event reporting additional description:

Adverse events were obtained through participant reporting or were elicited by specific questioning or examination of the participant.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Open-Label Sebelipase alfa

Reporting group description: -

Serious adverse events	Open-Label Sebelipase alfa		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 8 (12.50%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Surgical and medical procedures			
Cholecystectomy	Additional description: Cholecystectomy for cholelithiasis		
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Cholecystitis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Open-Label Sebelipase alfa		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)		

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lipoma			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Oral neoplasm benign			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Hyperaemia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	3		
Hypertension			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	5		
Orthostatic hypotension			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Chest discomfort			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
Chest pain			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	3		
Chills			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	3 / 8 (37.50%)		
occurrences (all)	3		

Non-cardiac chest pain subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	 2 / 8 (25.00%) 4 1 / 8 (12.50%) 1 1 / 8 (12.50%) 1		
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all) Seasonal allergy subjects affected / exposed occurrences (all)	 1 / 8 (12.50%) 1 1 / 8 (12.50%) 1		
Respiratory, thoracic and mediastinal disorders Choking subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Laryngeal oedema subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Rhinorrhoea	 1 / 8 (12.50%) 1 1 / 8 (12.50%) 3 2 / 8 (25.00%) 5 1 / 8 (12.50%) 4 1 / 8 (12.50%) 1 3 / 8 (37.50%) 4		

subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Blood creatinine increased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
C-reactive protein increased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Eosinophil count increased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Low density lipoprotein increased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Lymphocyte count increased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Mean cell volume increased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Prothrombin time abnormal			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Vitamin B12 decreased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
White blood cell count increased			

subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Cartilage injury			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Iliotibial band syndrome			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
Laceration			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Post procedural haemorrhage			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Procedural dizziness			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Procedural pain			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Sunburn			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Palpitations			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Tachycardia			

subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Nervous system disorders			
Amnesia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Clonic convulsion			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Dysarthria			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Dyskinesia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	5		
Headache			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Lethargy			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
Paraesthesia			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	3		
Syncope			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	4		
Tremor			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	4		
Ear and labyrinth disorders			
Ear pain			

subjects affected / exposed	3 / 8 (37.50%)		
occurrences (all)	3		
Eye disorders			
Blepharitis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
Conjunctivitis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Dry eye			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	3		
Eye pain			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Keratitis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Ocular hyperaemia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Vision blurred			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Abdominal pain			
subjects affected / exposed	5 / 8 (62.50%)		
occurrences (all)	16		
Abdominal pain upper			
subjects affected / exposed	3 / 8 (37.50%)		
occurrences (all)	8		
Diarrhoea			

subjects affected / exposed	4 / 8 (50.00%)		
occurrences (all)	12		
Dyspepsia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Faeces soft			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Flatulence			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Malocclusion			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	5 / 8 (62.50%)		
occurrences (all)	6		
Toothache			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Cholelithiasis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Granulomatous liver disease			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		

Hepatic pain subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 3		
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Dermal cyst subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 2		
Dermatitis acneiform subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Eczema subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Ephelides subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Pigmentation disorder subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Pruritus subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Rash macular subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Skin lesion subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Skin mass subjects affected / exposed occurrences (all)	3 / 8 (37.50%) 8		
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	4 / 8 (50.00%)		
occurrences (all)	7		
Bone pain			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Limb mass			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	3		
Muscle twitching			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	6		
Muscular weakness			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	3 / 8 (37.50%)		
occurrences (all)	3		
Myalgia			
subjects affected / exposed	3 / 8 (37.50%)		
occurrences (all)	3		
Neck mass			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Spinal pain			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Infections and infestations			
Abscess limb			

subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	1			
Bacterial vaginosis	Additional description: Affects only female participants.			
subjects affected / exposed[1]	1 / 2 (50.00%)			
occurrences (all)	3			
Cellulitis				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	1			
Ear infection				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	1			
Ear lobe infection				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	1			
Eye infection				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	1			
Folliculitis				
subjects affected / exposed	2 / 8 (25.00%)			
occurrences (all)	4			
Fungal skin infection				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	1			
Gastroenteritis				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	2			
Infected dermal cyst				
subjects affected / exposed	2 / 8 (25.00%)			
occurrences (all)	3			
Influenza				
subjects affected / exposed	2 / 8 (25.00%)			
occurrences (all)	3			
Lower respiratory tract infection				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	1			
Nasopharyngitis				

subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	4		
Pharyngitis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Rash pustular			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
Rhinitis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	5		
Subcutaneous abscess			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
Viral upper respiratory tract infection			
subjects affected / exposed	5 / 8 (62.50%)		
occurrences (all)	10		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Vitamin D deficiency			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		

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: This adverse event only affects female participants.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 January 2012	All changes in site-specific Protocol Amendment #2 were incorporated in this global amendment. This amendment included the following changes among others: • Study duration was updated to define a study period of 3 years. • Duration of investigational medicinal product (IMP) administration was updated to define a period of up to 3 years. • "End of Study" was added to Week 104 in order to define assessments to be completed at the final study visit. • Update with information from preclinical and other clinical studies • Addition / changes to methods + timepoints for analysis • Home infusion details were added for consistency with the synopsis + The criteria for determining a participant's eligibility for home infusions were further defined • IMP storage instructions were revised • A Per-Protocol Analysis Set was defined • The stopping rules were updated based on preliminary clinical data from LAL-CL01.
13 February 2013	• Added United States Adopted Name/International non-proprietary drug name. • Exploratory objective was added for evaluation of liver histology to understand long-term effects of sebelipase alfa on liver pathology. • Text clarified to reflect recent clinical experience regarding transient increases in serum lipid levels. • The protocol now allowed planned discontinuation of concomitant lipid-lowering medications (LLM) in participants whose lipid levels have normalised to the point that LLMs may no longer be indicated. • Clarified requirement for discussion with Sponsor and/or documentation around certain concomitant medications and major diet changes. • Stated rationale for obtaining unscheduled electrocardiograms (ECGs) if indicated based on cardiovascular symptoms. • Additional laboratory monitoring schedule of selected analytes in participants undergoing dose modification or change in LLM. • Clarified option for participants to transfer to local site for infusions and study assessments. • Defined inadequate clinical response. • Assessment of other potential causes of suboptimal response prior to dose increase. • Allowed reduction of dose to next lowest level in consultation with the Sponsor and possibly safety committee (SC). • Explained participant discontinuation criteria from the study, including continuation of immunoglobulin E (IgE)-positive participants. • Collection of serum samples for tryptase and antidrug antibodies for participants experiencing Grade 2 or higher suspected immune-mediated IARs. • Requirement for skin testing if IgE negative and IAR suspected to be immune mediated; if skin test positive, continuation only after SC review and agreement of Investigator. • Added optional liver biopsy to be performed anytime between Weeks 52 to 104. • Clarified management and post-IAR activities. • Specific medications were removed from mild IAR to allow for Investigator discretion. • Infusion rate titration recommendations added.

25 September 2014	• Extended the dosing duration to approximately 5 years, to allow collection of more long term data with sebelipase alfa. Updated the Schedule of Assessments to show that Year 2 assessments applied through Years 3, 4 and 5. • Removed infusion duration time, and revised other text pertaining to preparation and administration of IMP. • Updated information on clinical trial experience with sebelipase alfa, including a cross-reference to the Investigator Brochure where the most updated information resides. • Updated adverse event text and Sponsor information and revised stopping rules to align with other clinical trial protocols for this program.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/23348766