Clinical trial results:
An Open Label, Multicenter, Dose Escalation Study to Evaluate the Safety, Tolerability, Efficacy, Pharmacokinetics, and Pharmacodynamics of SBC-102 in Children with Growth Failure Due to Lysosomal Acid Lipase Deficiency

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	2011-000032-28
Trial protocol	GB FR DE IT IE
Global end of trial date	03 January 2018

Results information

Result version number	v1
This version publication date	20 July 2016
First version publication date	20 July 2016

Trial information

Trial identification

Sponsor protocol code	LAL-CL03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01371825
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alexion Pharmaceuticals Inc.
Sponsor organisation address	100 College Street, New Haven, CT, United States, 06510
Public contact	European Clinical Trial Information, Alexion Europe SAS, +33 147100606, clinicaltrials.eu@alexion.com
Scientific contact	European Clinical Trial Information, Alexion Europe SAS, +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	03 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 January 2018
Global end of trial reached?	Yes
Global end of trial date	03 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the effect of sebelipase alfa (SBC-102) therapy on survival at 12 months of age in children with growth failure due to lysosomal acid lipase (LAL) 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.
The participant's parent or legal guardian had the right to withdraw from the study at any time for any reason. The investigator and Sponsor also had the right to withdraw participants from the study at any time. Specific reasons for discontinuation included but were not restricted to the following:
- intercurrent illness
- adverse events
- protocol deviation or non-compliance
- termination of the study by the sponsor

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 May 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	4 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Turkey: 1
Country: Number of subjects enrolled	Egypt: 1
Country: Number of subjects enrolled	United States: 1
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Ireland: 1
Worldwide total number of subjects	9
EEA total number of subjects	6

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)	9
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 9 Principal Investigators at 9 centers participated in this study in the United Kingdom, United States, France, Turkey, Ireland, and Egypt.

Pre-assignment

Screening details:

To assess eligibility, participants were screened for a period of up to 3 weeks prior to enrollment. 11 total participants were screened, and 2 participants died during screening. The other 9 participants, all of whom were ≤ 8 months of age on the date of enrollment, met all eligibility criteria and were enrolled, treated, and analysed.

Period 1

Period 1 title	Open-label Sebelipase Alfa (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

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

Dosage and administration details:

All participants received intravenous (IV) infusions of sebelipase alfa during the open-label treatment period. Participants received a starting dose of 0.35 milligrams (mg)/kilogram (kg) once weekly (qw) and, after demonstrating acceptable safety and tolerability after at least 2 infusions at this dose, began receiving the per-protocol dose of 1 mg/kg qw. Thereafter, participants were to continue receiving a dose of 1 mg/kg qw for the duration of the treatment period. However, in the event of disease progression (based on protocol-defined criteria) at any time during treatment with 1 mg/kg qw, an individual participant could receive a dose increase to 3 mg/kg qw and, if necessary, a subsequent dose increase to 5 mg/kg qw (after review and approval by a Safety Committee [SC]). Participants receiving long-term treatment on a stable qw dose could be switched to an every other week (qow) dosing schedule at the same total dose (mg/kg) per infusion.

Number of subjects in period 1	Open-Label Sebelipase Alfa
Started	9
Received at Least 1 Dose of Study Drug	9
Completed	5
Not completed	4
Death	4

Baseline characteristics

Reporting groups

Reporting group title	Open-label Sebelipase Alfa

Reporting group description: -

Reporting group values	Open-label Sebelipase Alfa	Total	
Number of subjects	9	9	
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	9	9	
Age continuous			
The mean age (and range) at first dose of sebelipase alfa is presented.			
Units: months arithmetic mean full range (min-max)	 3.41 1.1 to 5.8	 -	
Gender categorical Units: Subjects			
Female	4	4	
Male	5	5	
Race Units: Subjects			
White	4	4	
Asian	1	1	
Black	1	1	
Unknown or not reported	3	3	
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	6	6	
Unknown or not reported	3	3	

Subject analysis sets

Subject analysis set title	Primary Efficacy Analysis Set (PES)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Evaluable participants in the PES, which included participants who received any amount of sebelipase alfa and who were ≤ 8 months of age on the date of their first infusion of sebelipase alfa. All 9 participants were evaluable.

Reporting group values	Primary Efficacy Analysis Set (PES)		
Number of subjects	9		
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	9		

Age continuous			
The mean age (and range) at first dose of sebelipase alfa is presented.			
Units: months			
arithmetic mean	3.41		
full range (min-max)	1.1 to 5.8		
Gender categorical			
Units: Subjects			
Female	4		
Male	5		
Race			
Units: Subjects			
White	4		
Asian	1		
Black	1		
Unknown or not reported	3		
Ethnicity			
Units: Subjects			
Hispanic or Latino	0		
Not Hispanic or Latino	6		
Unknown or not reported	3		

End points

End points reporting groups

Reporting group title	Open-Label Sebelipase Alfa
Reporting group description: -	
Subject analysis set title	Primary Efficacy Analysis Set (PES)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Evaluable participants in the PES, which included participants who received any amount of sebelipase alfa and who were ≤ 8 months of age on the date of their first infusion of sebelipase alfa. All 9 participants were evaluable.

Primary: Percentage Of Participants In The PES Surviving To 12 Months Of Age

End point title	Percentage Of Participants In The PES Surviving To 12 Months Of Age[1]

End point description:

The primary efficacy endpoint was the percentage of participants (%) in the PES who survived to at least 12 months of age.

End point type	Primary

End point timeframe:

Month 12

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: Single-arm estimate. The proportion of participants surviving to 12 months of age was calculated, along with an exact 95% confidence interval, based on the Clopper-Pearson method. Kaplan-Meier survival curves were also generated from birth to 12 months of age and from first infusion of sebelipase alfa to 12 months of age, and Kaplan-Meier methodology was used to estimate median age at death (as data permitted) and median survival past the first infusion of sebelipase alfa.

End point values	Primary Efficacy Analysis Set (PES)			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: % of subjects				
number (confidence interval 95%)	67 (29.9 to 92.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Of Participants Surviving Beyond 12 Months Of Age

End point title	Percentage Of Participants Surviving Beyond 12 Months Of Age

End point description:

The percentage of participants in the PES who survived to at least 18 months of age.

End point type	Secondary

End point timeframe:

From Baseline to Month 18, Month 24, Month 36, Month 48, and Month 60.

End point values	Primary Efficacy Analysis Set (PES)			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: % of subjects				
number (confidence interval 95%)				
Survival Through 18 Months of Age	56 (21.2 to 86.3)			
Survival Through 24 Months of Age	56 (21.2 to 86.3)			
Survival Through 36 Months of Age	56 (21.2 to 86.3)			
Survival Through 48 Months of Age	56 (21.2 to 86.3)			
Survival Through 60 Months of Age	43 (9.9 to 81.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Median Age At Death

End point title	Median Age At Death

End point description:

End point type	Secondary

End point timeframe:

From Baseline to Week 260

End point values	Primary Efficacy Analysis Set (PES)			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: age at death in months				
arithmetic mean (full range (min-max))	6.27 (2.8 to 15.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Effect On Growth Parameters (Weight For Age)

End point title	Effect On Growth Parameters (Weight For Age)

End point description:

changes from baseline in percentiles for weight-for-age (WFA)

End point type	Secondary

End point timeframe:

From week 0 to data cut-off

End point values	Open-Label Sebelipase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: number of subjects				
WFA increases across 2 major percentiles	1			
WFA increases across 3 major percentiles	2			
WFA increases across 4 major percentiles	1			
WFA increases across 5 major percentiles	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Of Participants With Stunting, Wasting, Or Underweight

End point title	Percentage Of Participants With Stunting, Wasting, Or Underweight

End point description:

The percentages of participants meeting criteria for the following dichotomous indicators of under nutrition were reported. These indicators included the following:

- Underweight (defined as < -2 SD from the median for weight-for-age);
- Wasting (defined as < -2 SD from the median for weight-for-length/weight-for-height; and
- Stunting (defined as < -2 SD from the median for length-for-age/height-for-age)

End point type	Secondary

End point timeframe:

From Baseline, Month 12, Month 24, Month 36, Month 48, and Month 60.

End point values	Primary Efficacy Analysis Set (PES)			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: number of subjects				
Stunting at Baseline (N=8)	4			
Wasting at Baseline (N=8)	2			
Underweight at Baseline (N=9)	2			
Stunting at Month 12 (N=4)	0			
Wasting at Month 12 (N=4)	0			
Underweight at Month 12 (N=4)	0			
Stunting at Month 24 (N=5)	0			
Wasting at Month 24 (N=5)	0			
Underweight at Month 24 (N=5)	0			
Stunting at Month 36 (N=5)	0			
Wasting at Month 36 (N=5)	0			
Underweight at Month 36 (N=5)	0			
Stunting at Month 48 (N=5)	0			
Wasting at Month 48 (N=5)	0			
Underweight at Month 48 (N=5)	0			
Stunting at Month 60 (N=2)	0			
Wasting at Month 60 (N=2)	0			
Underweight at Month 60 (N=2)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Serum Transaminases (ALT And AST) To Week 1 And Week 4

End point title	Change From Baseline In Serum Transaminases (ALT And AST) To Week 1 And Week 4

End point description:

Change from Baseline for alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

End point type	Secondary

End point timeframe:

ALT and AST change from Baseline were reported for Week 1 and Week 4.

End point values	Primary Efficacy Analysis Set (PES)			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: Median reduction from baseline (U/L)				
median (full range (min-max))				

ALT at week 1 (n=7)	-23 (-161 to 28)			
ALT at week 4 (n=5)	-33 (-226 to 4)			
AST at week 1 (n=6)	-43 (-327 to -12)			
AST at week 4 (n=4)	-55.5 (-427 to -20)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change In Serum Ferritin From Baseline To Week 1

End point title	Change In Serum Ferritin From Baseline To Week 1
End point description:	
Change from baseline in serum ferritin.	
End point type	Secondary
End point timeframe:	
Serum ferritin levels were reported from Baseline to Week 1	

End point values	Open-Label Sebelipase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: median reduction from baseline (µg/L)				
median (full range (min-max))	-122 (-6934 to -72)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number Of Participants Achieving And Maintaining Transfusion-free Hemoglobin Normalization

End point title	Number Of Participants Achieving And Maintaining Transfusion-free Hemoglobin Normalization
End point description:	
The number of participants achieving transfusion-free haemoglobin normalisation (TFHN) of ≥4 weeks at any time during the study (also referred to as short-term TFHN), and the proportion of participants who maintained TFHN for ≥13 weeks beginning at Week 6 (also referred to as sustained early TFHN).	
End point type	Secondary
End point timeframe:	
From Baseline to Week 260.	

End point values	Primary Efficacy Analysis Set (PES)			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: subjects reaching TFHN				
Achieved TFHN	6			
Maintained TFHN	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number Of Participants In The PES Surviving To 24 Months Of Age

End point title	Number Of Participants In The PES Surviving To 24 Months Of Age

End point description:

The number of participants in the PES who survived to at least 24 months of age was reported.

End point type	Secondary

End point timeframe:

From Week 0 to Month 24.

End point values	Primary Efficacy Analysis Set (PES)			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: number of subjects	5			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Week 0 to Week 260

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

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	9 / 9 (100.00%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events			
Investigations			
Weight decreased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Pallor			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Poor venous access			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Tachyarrhythmia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperthermia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Sudden cardiac death			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peritoneal haemorrhage			

subjects affected / exposed	1 / 9 (11.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Malabsorption				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hepatic failure				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Infections and infestations				
Bacterial pyelonephritis				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Catheter site infection				
subjects affected / exposed	2 / 9 (22.22%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	2 / 9 (22.22%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Device related sepsis				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				

subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Roseola			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bacteraemia	Additional description: Staphylococcal bacteraemia		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal toxaemia	Additional description: staphylococcal sepsis		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection	Additional description: Viral infection		
subjects affected / exposed	2 / 9 (22.22%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Adenovirus infection			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Amoebic dysentery			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Croup infectious			

subjects affected / exposed	1 / 9 (11.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rotavirus infection				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Failure to thrive				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Food intolerance				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acidosis	Additional description: metabolic acidosis			
subjects affected / exposed	1 / 9 (11.11%)			
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	9 / 9 (100.00%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Hypertension			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Pallor			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	5 / 9 (55.56%)		
occurrences (all)	69		
Chills			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	3		
Hyperthermia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Catheter site rash			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Disease progression			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Infusion Site Extravasation			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Feeling abnormal			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Gait disturbance			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Granuloma			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Infusion site oedema			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Irritability			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Asthenia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Catheter site pain			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Catheter site swelling			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Swelling			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Reproductive system and breast disorders			
Penile blister			
subjects affected / exposed[1]	1 / 5 (20.00%)		
occurrences (all)	1		
Genital rash			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 9 (55.56%)		
occurrences (all)	33		
Rhinorrhoea			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	14		
Pharyngeal erythema			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Respiratory failure			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Sneezing			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Tonsillar disorder			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Use of accessory respiratory muscles			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Wheezing			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Respiratory distress			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Productive cough			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Tachypnoea			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Tonsillar hypertrophy			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Irritability			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Emotional disorder			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Product issues			
Device dislocation			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Device malfunction			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Investigations			
Staphylococcus test positive			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Blood immunoglobulin A abnormal			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Blood immunoglobulin G abnormal			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Blood lactate dehydrogenase increased			

subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Blood potassium decreased				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Blood urea increased				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Body temperature increased				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Lymphocyte count abnormal				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Lymphocyte count increased				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Monocyte count increased				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Neutrophil count increased				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Norovirus test positive				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Oxygen saturation decreased				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Platelet count increased				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Respiratory syncytial virus test positive				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			

Serum ferritin increased				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Transaminases increased				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Urine albumin/creatinine ratio increased				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Urine output decreased				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Vitamin D decreased				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Adenovirus test positive				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Blood immunoglobulin G decreased				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Blood albumin decreased				
subjects affected / exposed	2 / 9 (22.22%)			
occurrences (all)	3			
Clostridium test positive				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Parasite stool test positive				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Pseudomonas test positive				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Respirovirus test positive				

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Vitamin E decreased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Protein total decreased			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Endotracheal intubation complication			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Limb injury			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Mouth injury			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Post procedural discharge			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	3		
Postoperative ileus			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Fall			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Head injury			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Laceration			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Stoma site inflammation			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Tooth injury			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	5		
Bradycardia			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Cardiovascular disorder			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Nervous system disorders			
Hypotonia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 9 (44.44%)		
occurrences (all)	6		
Thrombocytopenia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		

Lymphadenopathy subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Lymphopenia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Iron deficiency anaemia subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 3		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 4		
Middle ear inflammation subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 2		
Pupillary disorder subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all)	6 / 9 (66.67%) 53		
Diarrhoea subjects affected / exposed occurrences (all)	6 / 9 (66.67%) 55		
Abdominal distension subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 5		
Nausea subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 2		
Teething			

subjects affected / exposed	3 / 9 (33.33%)			
occurrences (all)	4			
Ascites				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Faeces discoloured				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Gastrooesophageal reflux disease				
subjects affected / exposed	2 / 9 (22.22%)			
occurrences (all)	2			
Haematochezia				
subjects affected / exposed	2 / 9 (22.22%)			
occurrences (all)	3			
Post-tussive vomiting				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	3			
Retching				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Tongue discolouration				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Umbilical hernia				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Abdominal discomfort				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Abdominal pain upper				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Abdominal pain				
subjects affected / exposed	3 / 9 (33.33%)			
occurrences (all)	4			
Constipation				

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Dental caries			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Enteritis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Flatulence			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Gastritis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Hyperbilirubinaemia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Dermatitis diaper			
subjects affected / exposed	4 / 9 (44.44%)		
occurrences (all)	7		
Urticaria			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	10		
Rash			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	10		
Eczema			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	3		
Pruritus generalised			

subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Umbilical erythema subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Petechiae subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Pruritus subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Rash macular subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Skin discolouration subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Skin irritation subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Xanthoma subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Erythema subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2		
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Endocrine disorders Adrenal insufficiency subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Musculoskeletal and connective tissue disorders			

Myalgia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Infections and infestations			
Rhinitis			
subjects affected / exposed	5 / 9 (55.56%)		
occurrences (all)	36		
Catheter site infection			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Device related infection			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	4		
Nasopharyngitis			
subjects affected / exposed	5 / 9 (55.56%)		
occurrences (all)	14		
Ear infection viral			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	3		
Bronchiolitis			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Gastroenteritis			
subjects affected / exposed	4 / 9 (44.44%)		
occurrences (all)	11		
Pharyngitis			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	6		
Varicella			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	3		
Bacterial infection			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Bronchitis			

subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Candida nappy rash				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Escherichia urinary tract infection				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Eyelid infection				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Fungal infection				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Metapneumovirus infection				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Oral candidiasis				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Oral fungal infection				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Oral herpes				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Otitis media				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	2			
Post procedural infection				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Rash pustular				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Staphylococcal skin infection				

subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Upper respiratory tract infection				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Viral infection				
subjects affected / exposed	3 / 9 (33.33%)			
occurrences (all)	5			
Angular cheilitis				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Croup infectious				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	2			
Gastroenteritis viral				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Infectious mononucleosis				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Influenza				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Scarlet fever				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Stoma site candida				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Tonsillitis				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Conjunctivitis				
subjects affected / exposed	2 / 9 (22.22%)			
occurrences (all)	2			
Fungal skin infection				

subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Hand-foot-and-mouth disease			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Urinary tract infection			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Ear infection			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	4		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	5		
Dehydration			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Hypercalcaemia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Hyperglycaemia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Hypernatraemia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Hypocalcaemia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Hypophosphataemia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Hypoproteinaemia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		

Iron deficiency			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Metabolic acidosis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Vitamin D deficiency			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	4		
Hypovolaemia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Vitamin A deficiency			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Vitamin E deficiency			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Vitamin K deficiency			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	5		

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 male participants.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 February 2011	This amendment included the following major changes: • The system for grading adverse event (AE) severity was changed from Division of Acquired Immunodeficiency Syndrome to NCI CTCAE based on a regulatory request. • Addition of rules for stopping dosing in an individual participant or all study participants.
20 May 2011	All changes in country-specific Protocol Amendment 2 were incorporated in this global amendment, with one clarification (see first bullet below). This amendment included the following major changes: • Further clarified the first criterion in the definition of growth failure. • Amended the definition of extreme prematurity from < 32 weeks gestational age at birth to < 36 weeks gestational age at birth. • Added birth weight to the list of demographic information to be collected. • Allowed the dose (mg) of sebelipase alfa to be determined based on a participant's last available weight measurement if weight could not be obtained on the day of the infusion due to the participant's condition. • Allowed for a screening period of < 7 days, to minimise the delay in treatment initiation, which could be important for severe cases. • Allowed for replacement of participants who had received fewer than 4 infusions of sebelipase alfa.
20 September 2011	This global amendment included the following: • Clarifications to safety reporting guidelines made to comply with local regulations. • Nonclinical and clinical information for sebelipase alfa was also updated.
05 April 2012	This amendment merged study LAL-CL03 with its extension study, LAL-CL05, under a single protocol. Study LAL-CL03 was originally designed as a safety trial with a limited 4-month treatment period. After additional nonclinical chronic toxicology data and extended clinical experience in adults became available, the Sponsor opened LAL-CL05 as an extension study, to permit participants who had been receiving treatment in LAL-CL03 (or under an expanded access program) to continue receiving sebelipase alfa without interruption, and to evaluate the long-term safety and efficacy of sebelipase alfa in these participants, including an analysis of survival. In addition, all changes in country-specific Protocol Amendment 4 and Protocol Amendment 5 were incorporated in this global amendment.
23 October 2012	This amendment included the following major changes: • Added the option of a qow dosing schedule for participants who were on treatment for at least 96 weeks and had been on a stable dose for at least 24 weeks. • Modified the definition of suboptimal response to distinguish between early (first 3 months of treatment) and late (beyond 3 months of treatment) suboptimal response -- and added criteria for late suboptimal response. • Added anti-drug antibody (ADA) and tryptase testing in participants who experienced a moderate or severe infusion associated reaction (IAR). • Clarified that continuation of hospitalisation for trial purposes in participants who were already hospitalised at the start of the study due to severity of disease, would not be considered a serious adverse event (SAE).

05 February 2013	This amendment was written to allow enrollment of a participant who had not yet met the criteria for growth failure if (a) the investigator has substantial clinical concerns based on evidence of the rapid disease progression requiring urgent medical intervention and (b) the participant had an older (biological) sibling who had a documented rapidly progressive course of LAL Deficiency with growth failure before 6 months of age. This exception was included as a footnote to the growth failure inclusion criterion, and further specified the process the Investigator was to follow to obtain approval for enrollment of such a participant.
19 March 2013	This amendment included the following major change: • Modified the language introduced in Amendment 8. Specifically, the footnote to the growth failure inclusion criterion was revised to remove the requirement that the participant have an older (biological) sibling who had a documented rapidly progressive course of LAL Deficiency with growth failure before 6 months of age.
24 January 2014	This amendment included the following major changes: • Extended the treatment period for each participant up to maximum of 4 years. • Refined the definition of suboptimal response, and specified that the evaluation of the suboptimal response was done in consultation with the SC. • Added an optional dose increase to 5 mg/kg qw for any participant who had a continued suboptimal response at 3 mg/kg (after at least 4 infusions) in association with the presence of neutralising antibodies. • Added annual magnetic resonance imaging, monthly weights after Week 24, and an optional liver biopsy.
21 November 2014	This amendment included the following changes: • Extended dosing period to up to 5 years. • Removed the terminology "suboptimal response" and replaced with criteria for dose escalation. • Added the collection of serum lipid, serum liver, hematology, chemistry, ferritin, and high-sensitivity C-reactive protein labs prior to any dose change and serum lipid and serum liver 4, 8, and 12 weeks following any dose change. • Removed the terminology "total and functional area scores" relating to the Denver II. • Modified safety end points characterizing ADAs to remove reference to immunoglobulin G, seroconversion, and tolerization. • Removed infusion duration time, infusion rate table, and added in the final concentration of the infusion. •Antidrug antibody collection time points were updated from every 24 weeks following Week 24 to every 12 weeks following Week 24. •Revised the text on infusion associated reaction (IAR) management. •Revised the stopping rules to remove stopping rule for an individual participant for grade 1 and 2 IARs, for grade 4 AEs. •Removed specific stopping rule to pause dosing in all participants in the case of 3 or more participants with similar SAEs and in 3 or more participants with recurrent, unmanageable severe or higher IARs.
05 January 2016	This amendment included the following minor changes: • Updated to the Sponsor information and SAE Reporting information (updated where to report SAEs, such as phone numbers)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported