



Clinical trial results:

An Open-Label, Multicenter, Multinational Study of the Safety, Efficacy and Pharmacokinetics of Asfotase alfa (human recombinant tissue nonspecific alkaline phosphatase fusion protein) in Infants and Children 5 Years of Age with Hypophosphatasia (HPP)

Summary

EudraCT number	2010-019850-42
Trial protocol	DE GB IT ES FR
Global end of trial date	26 April 2017

Results information

Result version number	v1 (current)
This version publication date	11 November 2017
First version publication date	11 November 2017

Trial information

Trial identification

Sponsor protocol code	ENB-010-10
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01176266
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alexion Pharmaceuticals
Sponsor organisation address	100 College Street, New Haven, United States, 06510
Public contact	European Clinical Trial Information, ALEXION EUROPE SAS, +33 14710 0606, clinicaltrials.eu@alexion.com
Scientific contact	European Clinical Trial Information, ALEXION EUROPE SAS, +33 14710 0606, 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)	EMA-000987-PIP01-10
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	26 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 September 2016
Global end of trial reached?	Yes
Global end of trial date	26 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the following:

- Effect of Asfotase alfa treatment on skeletal manifestations of HPP as measured by radiographs using a qualitative Radiographic Global Impression of Change (RGI-C) scale for all treated patients
- Safety and tolerability of repeated subcutaneous (SC) injections of Asfotase alfa for all treated patients

Protection of trial subjects:

No specific measure

Background therapy: -

Evidence for comparator:

No comparator was used

Actual start date of recruitment	26 July 2010
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	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	United States: 21
Country: Number of subjects enrolled	Turkey: 4
Country: Number of subjects enrolled	Japan: 5
Country: Number of subjects enrolled	Saudi Arabia: 1
Country: Number of subjects enrolled	Russian Federation: 1
Country: Number of subjects enrolled	Australia: 1
Worldwide total number of subjects	69
EEA total number of subjects	25

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	4
Infants and toddlers (28 days-23 months)	35
Children (2-11 years)	30
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:

The main criteria for inclusion in the study were male and female patients less than or equal to 5 years of age with a documented diagnosis of infantile onset hypophosphatasia (HPP) who were otherwise medically stable. Patients must have had onset of HPP signs/symptoms prior to 6 months of age.

Pre-assignment

Screening details:

After a Screening visit to assess their eligibility, patients were to receive 6 mg/kg per week of asfotase alfa, administered SC as either 1 mg/kg 6 times per week or 2 mg/kg 3 times per week.

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:

N/A

Arms

Arm title	Asfotase Alfa
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Arm description:

A total of 6 mg/kg/week of asfotase alfa administered by SC injection (either 1 mg/kg asfotase alfa 6 times per week, or 2 mg/kg asfotase alfa 3 times per week)

Arm type	Experimental
Investigational medicinal product name	Asfotase Alfa
Investigational medicinal product code	
Other name	ENB-0040
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Subcutaneous use, Intravenous use

Dosage and administration details:

Patients received a total of 6 mg/kg/week of asfotase alfa administered by SC injection, either 1 mg/kg asfotase alfa 6 times per week or 2 mg/kg asfotase alfa 3 times per week.

Number of subjects in period 1	Asfotase Alfa
Started	69
Completed	60
Not completed	9
Adverse event, serious fatal	6
Consent withdrawn by subject	3

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial
Reporting group description: -	

Reporting group values	Overall Trial	Total	
Number of subjects	69	69	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	4	4	
Infants and toddlers (28 days-23 months)	35	35	
Children (2-11 years)	30	30	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Full Analysis Set (defined as all patients who received any asfotase alfa treatment)			
Units: weeks			
arithmetic mean	113.42		
standard deviation	± 108.912	-	
Gender categorical			
Units: Subjects			
Female	36	36	
Male	33	33	
Ethnicity			
Units: Subjects			
Hispanic or Latino	1	1	
Not Hispanic or Latino	63	63	
Unknown or Not Reported	5	5	
Race			
Units: Subjects			
Asian	7	7	
White	54	54	
Unknown or Not Reported	8	8	

End points

End points reporting groups

Reporting group title	Asfotase Alfa
Reporting group description:	
A total of 6 mg/kg/week of asfotase alfa administered by SC injection (either 1 mg/kg asfotase alfa 6 times per week, or 2 mg/kg asfotase alfa 3 times per week)	

Primary: Effect of Asfotase Alfa Treatment on Skeletal Manifestations of Hypophosphatasia (HPP)

End point title	Effect of Asfotase Alfa Treatment on Skeletal Manifestations of Hypophosphatasia (HPP) ^[1]
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End point description:

The effect of asfotase alfa treatment on skeletal manifestations of HPP (i.e., change in rickets severity) was measured by radiographs using a qualitative Radiographic Global Impression of Change (RGI-C) scale. Skeletal radiographs obtained at Week 48 were compared with skeletal radiographs obtained before initiation of treatment. The RGI-C is a 7-point rating scale that ranges from -3 (indicative of severe worsening of HPP-associated rickets) to +3 (indicative of complete or near complete healing of HPP-associated rickets).

End point type	Primary
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End point timeframe:

From Baseline to Week 48

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: The system EudraCT does not allow entering for statistical analysis for single arm studies. Thus, the analysis was removed in order to resolve the IT 'error'

End point values	Asfotase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	69			
Units: Units on a scale				
median (full range (min-max))	2.00 (-2.33 to 3.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety and Tolerability of Repeated Subcutaneous (SC) Injections of Asfotase Alfa

End point title	Safety and Tolerability of Repeated Subcutaneous (SC) Injections of Asfotase Alfa
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End point description:

Safety and tolerability of repeated subcutaneous (SC) injections of asfotase alfa for all treated patients was assessed by the number of patients with 1 or more treatment-emergent adverse event.

End point type	Secondary
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End point timeframe:

Up to 72 months or until regulatory approval. Patients received study drug for a median duration of 829.0 days, with a range from 6 to 2116 days (ie, from 0.9 week to 5.8 years).

End point values	Asfotase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	69			
Units: Participants	69			

Statistical analyses

No statistical analyses for this end point

Secondary: Effect of Asfotase Alfa Treatment on Skeletal Manifestations of Hypophosphatasia (HPP)

End point title	Effect of Asfotase Alfa Treatment on Skeletal Manifestations of Hypophosphatasia (HPP)
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End point description:

The effect of asfotase alfa treatment on skeletal manifestations of HPP was measured by radiographs using a qualitative Radiographic Global Impression of Change (RGI-C) scale from Baseline to the last assessment for each patient.

End point type	Secondary
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End point timeframe:

Up to 72 Months or regulatory approval in the country of residence. Patients received study drug for a median duration of 829.0 days, with a range from 6 to 2116 days (ie, from 0.9 week to 5.8 years).

End point values	Asfotase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: units on a scale				
median (full range (min-max))	2.33 (-2.67 to 3.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Effect of Asfotase Alfa Treatment on Ventilator-free Survival (Week 288)

End point title	Effect of Asfotase Alfa Treatment on Ventilator-free Survival (Week 288)
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End point description:

For patients who were not on respiratory support at the time of enrollment, the Kaplan-Meier estimate of ventilator-free survival at the end of the study

End point type	Secondary
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End point timeframe:

Up to 72 months or until regulatory approval in the country of residence. Patients received study drug

for a median duration of 829.0 days, with a range from 6 to 2116 days (ie, from 0.9 week to 5.8 years).

End point values	Asfotase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Kaplan-Meier estimate of survival				
number (not applicable)	0.84			

Statistical analyses

No statistical analyses for this end point

Secondary: Effect of Asfotase Alfa Treatment on Respiratory Function

End point title	Effect of Asfotase Alfa Treatment on Respiratory Function
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End point description:

Effect of asfotase alfa treatment on respiratory function as measured by the shift in proportion of patients requiring respiratory support at their last assessment compared with Baseline.

Baseline: Baseline assessment before initiation of asfotase alfa

Asfotase Alfa - Without Respiratory Support at Baseline: Results at End of Study for Those Without Respiratory Support at Baseline (Last Assessment for Each Patient)

Asfotase Alfa - With Respiratory Support at Baseline: Results at End of Study for Those Without Respiratory Support at Baseline (Last Assessment for Each Patient)

End point type	Secondary
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End point timeframe:

Up to 72 months or until regulatory approval in the country of residence. Patients received study drug for a median duration of 829.0 days, with a range from 6 to 2116 days (ie, from 0.9 week to 5.8 years).

End point values	Asfotase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	69			
Units: Participants				
No respiratory support	45			
Supplemental oxygen	6			
Biphasic positive airway pressure	0			
Continuous positive airway pressure	4			
Mechanical ventilation	13			
Other	1			

Attachments (see zip file)	Measured Values/Measured Values.xlsx
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Statistical analyses

No statistical analyses for this end point

Secondary: Effect of Asfotase Alfa Treatment on Physical Growth - Length/Height Z-scores Change From Baseline

End point title	Effect of Asfotase Alfa Treatment on Physical Growth - Length/Height Z-scores Change From Baseline
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End point description:

Effect of asfotase alfa treatment on physical growth as measured by change from Baseline to last assessment for each patient in length/height Z-scores

End point type	Secondary
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End point timeframe:

Up to 72 months or until regulatory approval in the country of residence. Patients received study drug for a median duration of 829.0 days, with a range from 6 to 2116 days (ie, from 0.9 week to 5.8 years).

End point values	Asfotase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: Z-Scores				
median (full range (min-max))	0.5 (-4 to 4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Effect of Asfotase Alfa Treatment on Physical Growth - Weight Z-scores Change From Baseline

End point title	Effect of Asfotase Alfa Treatment on Physical Growth - Weight Z-scores Change From Baseline
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End point description:

Effect of asfotase alfa treatment on physical growth as measured by change from Baseline to last assessment for each patient in weight Z-scores

End point type	Secondary
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End point timeframe:

Up to 72 months or until regulatory approval in the country of residence. Patients received study drug for a median duration of 829.0 days, with a range from 6 to 2116 days (ie, from 0.9 week to 5.8 years).

End point values	Asfotase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Z-Scores				
median (full range (min-max))	1.0 (-5 to 6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Effect of Asfotase Alfa on Biomarkers - Plasma Inorganic Pyrophosphate (PPi) Change From Baseline

End point title	Effect of Asfotase Alfa on Biomarkers - Plasma Inorganic Pyrophosphate (PPi) Change From Baseline
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End point description:

Effect of asfotase alfa on PPi as measured by change from Baseline to last assessment for each patient

End point type	Secondary
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End point timeframe:

Up to 72 months or until regulatory approval in the country of residence. Patients received study drug for a median duration of 829.0 days, with a range from 6 to 2116 days (ie, from 0.9 week to 5.8 years).

End point values	Asfotase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	63			
Units: uM				
median (full range (min-max))	-2.460 (-12.18 to 22.47)			

Statistical analyses

No statistical analyses for this end point

Secondary: Effect of Asfotase Alfa on Biomarkers - Plasma Pyridoxal-5' Phosphate (PLP) Change From Baseline

End point title	Effect of Asfotase Alfa on Biomarkers - Plasma Pyridoxal-5' Phosphate (PLP) Change From Baseline
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End point description:

Effect of asfotase alfa on PLP as measured by change from Baseline to last assessment for each patient

End point type	Secondary
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End point timeframe:

Up to 72 months or until regulatory approval in the country of residence. Patients received study drug for a median duration of 829.0 days, with a range from 6 to 2116 days (ie, from 0.9 week to 5.8 years).

End point values	Asfotase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: ng/mL				
median (full range (min-max))	-395.40 (-23836.0 to 2400.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Effect of Asfotase Alfa on Serum Parathyroid Hormone (PTH) - Change From Baseline

End point title	Effect of Asfotase Alfa on Serum Parathyroid Hormone (PTH) - Change From Baseline
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End point description:

Effect of asfotase alfa on serum PTH as measured by change from Baseline to last assessment for each patient

End point type	Secondary
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End point timeframe:

Up to 72 months or until regulatory approval in the country of residence. Patients received study drug for a median duration of 829.0 days, with a range from 6 to 2116 days (ie, from 0.9 week to 5.8 years).

End point values	Asfotase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	47			
Units: pmol/L				
median (full range (min-max))	0.70 (-4.7 to 5.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Effect of Asfotase Alfa Treatment on Tooth Loss

End point title	Effect of Asfotase Alfa Treatment on Tooth Loss
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End point description:

Effect of asfotase alfa treatment on tooth loss assessed by the proportion of patients who experienced tooth loss during the study

End point type	Secondary
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End point timeframe:

Up to 72 months or until regulatory approval in the country of residence. Patients received study drug for a median duration of 829.0 days, with a range from 6 to 2116 days (ie, from 0.9 week to 5.8 years).

End point values	Asfotase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	69			
Units: Participants	42			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) Properties of Asfotase Alfa

End point title	Pharmacokinetic (PK) Properties of Asfotase Alfa
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End point description:

The PK properties of asfotase alfa

End point type	Secondary
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End point timeframe:

Up to 72 months or until regulatory approval in the country of residence. Patients received study drug for a median duration of 829.0 days, with a range from 6 to 2116 days (ie, from 0.9 week to 5.8 years).

End point values	Asfotase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[2]			
Units: Participants				

Notes:

[2] - No Data was reported for this end point.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from the time the parents/legal guardians signed the informed consent form through completion of the patients participation in the study.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	13.0
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Reporting groups

Reporting group title	Asfotase Alfa
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Reporting group description: -

Serious adverse events	Asfotase Alfa		
Total subjects affected by serious adverse events			
subjects affected / exposed	50 / 69 (72.46%)		
number of deaths (all causes)	9		
number of deaths resulting from adverse events	9		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Cranial operation			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Medical device removal			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tracheal operation			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Tracheostomy			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wean from ventilator			
subjects affected / exposed	1 / 69 (1.45%)		
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 / 69 (1.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Device dislocation			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injection site erythema			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Irritability			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Oedema			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	6 / 69 (8.70%)		
occurrences causally related to treatment / all	2 / 14		
deaths causally related to treatment / all	0 / 0		

Immune system disorders			
Anaphylactoid reaction			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Drug hypersensitivity			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Adenoidal hypertrophy			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Apnoea			
subjects affected / exposed	3 / 69 (4.35%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Asthma			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atelectasis			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bronchospasm			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Collapse of lung				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	2 / 69 (2.90%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Obstructive airways disorder				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	2 / 69 (2.90%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary hypertension				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory arrest				

subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory disorder			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Respiratory distress			
subjects affected / exposed	3 / 69 (4.35%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	3 / 69 (4.35%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Upper respiratory tract inflammation			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Breath holding			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Staring			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Aspiration tracheal			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
CSF pressure			

subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterovirus test positive				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic enzyme increased				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Human rhinovirus test positive				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neurological examination abnormal				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Nuclear magnetic resonance imaging				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oxygen saturation decreased				
subjects affected / exposed	4 / 69 (5.80%)			
occurrences causally related to treatment / all	0 / 14			
deaths causally related to treatment / all	0 / 0			
Respiratory rate increased				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory syncytial virus test positive				

subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Weight decreased			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Abdominal wound dehiscence			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Brain herniation			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Endotracheal intubation complication			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Eye injury			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Feeding tube complication			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	3 / 69 (4.35%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			

subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Incorrect dose administered			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rib fracture			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Arnold-Chiari malformation			
subjects affected / exposed	3 / 69 (4.35%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 0		
Craniosynostosis			
subjects affected / exposed	13 / 69 (18.84%)		
occurrences causally related to treatment / all	1 / 13		
deaths causally related to treatment / all	0 / 0		
Hypophosphatasia			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bradycardia			
subjects affected / exposed	3 / 69 (4.35%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 0		

Cardiac arrest			
subjects affected / exposed	3 / 69 (4.35%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Cardio-respiratory arrest			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Cardiopulmonary failure			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cyanosis			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Wolff-Parkinson-White syndrome			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Brain oedema			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Convulsion			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Encephalitis			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile convulsion			

subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Haemorrhagic stroke			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hydrocephalus			
subjects affected / exposed	3 / 69 (4.35%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Intracranial hypotension			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intracranial pressure increased			
subjects affected / exposed	3 / 69 (4.35%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Motor developmental delay			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Motor dysfunction			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neurological symptom			

subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Petit mal epilepsy			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syringomyelia			
subjects affected / exposed	3 / 69 (4.35%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Coagulopathy			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Optic neuropathy			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Pancreatitis acute			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumatosis intestinalis			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rectal prolapse			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	3 / 69 (4.35%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hyperparathyroidism tertiary			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint contracture			

subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteopenia			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pathological fracture			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Adenoviral upper respiratory infection			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bacteraemia			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Beta haemolytic streptococcal infection			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchiolitis			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			

subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile colitis				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Corona virus infection				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	2 / 69 (2.90%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Enterobacter infection				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	2 / 69 (2.90%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis rotavirus				
subjects affected / exposed	2 / 69 (2.90%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis viral				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				

subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Meningitis staphylococcal				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Otitis media				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Parainfluenzae virus infection				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	8 / 69 (11.59%)			
occurrences causally related to treatment / all	1 / 9			
deaths causally related to treatment / all	0 / 3			
Pneumonia viral				
subjects affected / exposed	3 / 69 (4.35%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Postoperative wound infection				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pseudomonas infection				

subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory syncytial virus infection				
subjects affected / exposed	2 / 69 (2.90%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection viral				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rhinovirus infection				
subjects affected / exposed	2 / 69 (2.90%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	2 / 69 (2.90%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Serratia infection				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Serratia sepsis				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal infection				

subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal sepsis			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stenotrophomonas infection			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 69 (2.90%)		
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 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dystrophic calcification			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Failure to thrive			

subjects affected / exposed	2 / 69 (2.90%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Feeding disorder				
subjects affected / exposed	2 / 69 (2.90%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Fluid overload				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Food intolerance				
subjects affected / exposed	4 / 69 (5.80%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Hyperkalaemia				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypernatraemia				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperphosphataemia				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypervolaemia				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoalbuminaemia				

subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypophagia			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Asfotase Alfa		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	68 / 69 (98.55%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	4		
General disorders and administration site conditions			
Catheter site erythema			
subjects affected / exposed	5 / 69 (7.25%)		
occurrences (all)	16		
Catheter site inflammation			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	5		
Device occlusion			

subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	8		
Injection site atrophy			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	15		
Injection site discolouration			
subjects affected / exposed	12 / 69 (17.39%)		
occurrences (all)	43		
Injection site erythema			
subjects affected / exposed	33 / 69 (47.83%)		
occurrences (all)	223		
Injection site haematoma			
subjects affected / exposed	10 / 69 (14.49%)		
occurrences (all)	22		
Injection site induration			
subjects affected / exposed	11 / 69 (15.94%)		
occurrences (all)	44		
Injection site pain			
subjects affected / exposed	8 / 69 (11.59%)		
occurrences (all)	22		
Injection site papule			
subjects affected / exposed	5 / 69 (7.25%)		
occurrences (all)	91		
Injection site pruritus			
subjects affected / exposed	6 / 69 (8.70%)		
occurrences (all)	14		
Injection site rash			
subjects affected / exposed	5 / 69 (7.25%)		
occurrences (all)	5		
Injection site reaction			
subjects affected / exposed	8 / 69 (11.59%)		
occurrences (all)	13		
Injection site swelling			
subjects affected / exposed	7 / 69 (10.14%)		
occurrences (all)	21		
Irritability			

subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	6		
Pyrexia			
subjects affected / exposed	47 / 69 (68.12%)		
occurrences (all)	131		
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	6 / 69 (8.70%)		
occurrences (all)	12		
Cough			
subjects affected / exposed	17 / 69 (24.64%)		
occurrences (all)	34		
Dyspnoea			
subjects affected / exposed	8 / 69 (11.59%)		
occurrences (all)	30		
Oropharyngeal pain			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	6		
Respiratory distress			
subjects affected / exposed	6 / 69 (8.70%)		
occurrences (all)	7		
Rhinorrhoea			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	4		
Tachypnoea			
subjects affected / exposed	6 / 69 (8.70%)		
occurrences (all)	7		
Tracheomalacia			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	5		
Use of accessory respiratory muscles			
subjects affected / exposed	7 / 69 (10.14%)		
occurrences (all)	16		
Wheezing			

subjects affected / exposed occurrences (all)	5 / 69 (7.25%) 6		
Psychiatric disorders Agitation subjects affected / exposed occurrences (all)	4 / 69 (5.80%) 11		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) Aspartate aminotransferase increased subjects affected / exposed occurrences (all) Oxygen saturation decreased subjects affected / exposed occurrences (all) Vitamin D decreased subjects affected / exposed occurrences (all)	6 / 69 (8.70%) 8 5 / 69 (7.25%) 6 5 / 69 (7.25%) 54 4 / 69 (5.80%) 6		
Injury, poisoning and procedural complications Arthropod bite subjects affected / exposed occurrences (all) Contusion subjects affected / exposed occurrences (all) Fall subjects affected / exposed occurrences (all) Procedural pain subjects affected / exposed occurrences (all) Rib fracture subjects affected / exposed occurrences (all) Tooth fracture	5 / 69 (7.25%) 5 10 / 69 (14.49%) 21 7 / 69 (10.14%) 9 5 / 69 (7.25%) 6 5 / 69 (7.25%) 5		

subjects affected / exposed occurrences (all)	4 / 69 (5.80%) 4		
Congenital, familial and genetic disorders Congenital bowing of long bones subjects affected / exposed occurrences (all) Craniosynostosis subjects affected / exposed occurrences (all)	5 / 69 (7.25%) 6 10 / 69 (14.49%) 11		
Cardiac disorders Bradycardia subjects affected / exposed occurrences (all) Tachycardia subjects affected / exposed occurrences (all)	4 / 69 (5.80%) 7 6 / 69 (8.70%) 16		
Nervous system disorders Cerebral ventricle dilatation subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	4 / 69 (5.80%) 6 10 / 69 (14.49%) 22		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Lymphadenopathy subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all)	9 / 69 (13.04%) 13 5 / 69 (7.25%) 7 4 / 69 (5.80%) 4		
Ear and labyrinth disorders Cerumen impaction			

subjects affected / exposed	5 / 69 (7.25%)		
occurrences (all)	11		
Eye disorders			
Conjunctivitis			
subjects affected / exposed	8 / 69 (11.59%)		
occurrences (all)	16		
Papilloedema			
subjects affected / exposed	5 / 69 (7.25%)		
occurrences (all)	8		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	7 / 69 (10.14%)		
occurrences (all)	7		
Constipation			
subjects affected / exposed	16 / 69 (23.19%)		
occurrences (all)	37		
Dental caries			
subjects affected / exposed	7 / 69 (10.14%)		
occurrences (all)	11		
Diarrhoea			
subjects affected / exposed	20 / 69 (28.99%)		
occurrences (all)	35		
Gastrooesophageal reflux disease			
subjects affected / exposed	9 / 69 (13.04%)		
occurrences (all)	10		
Teething			
subjects affected / exposed	5 / 69 (7.25%)		
occurrences (all)	10		
Tooth loss			
subjects affected / exposed	41 / 69 (59.42%)		
occurrences (all)	109		
Toothache			
subjects affected / exposed	5 / 69 (7.25%)		
occurrences (all)	8		
Vomiting			

subjects affected / exposed occurrences (all)	30 / 69 (43.48%) 92		
Hepatobiliary disorders Hepatomegaly subjects affected / exposed occurrences (all)	4 / 69 (5.80%) 4		
Skin and subcutaneous tissue disorders Dermatitis diaper subjects affected / exposed occurrences (all) Dry skin subjects affected / exposed occurrences (all) Eczema subjects affected / exposed occurrences (all) Erythema subjects affected / exposed occurrences (all) Excessive granulation tissue subjects affected / exposed occurrences (all) Granuloma skin subjects affected / exposed occurrences (all) Heat rash subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	10 / 69 (14.49%) 18 8 / 69 (11.59%) 10 7 / 69 (10.14%) 14 6 / 69 (8.70%) 8 5 / 69 (7.25%) 6 4 / 69 (5.80%) 7 4 / 69 (5.80%) 5 11 / 69 (15.94%) 23		
Renal and urinary disorders Nephrocalcinosis subjects affected / exposed occurrences (all)	5 / 69 (7.25%) 5		
Musculoskeletal and connective tissue disorders			

Bone disorder subjects affected / exposed occurrences (all)	4 / 69 (5.80%) 23		
Knee deformity subjects affected / exposed occurrences (all)	5 / 69 (7.25%) 5		
Kyphosis subjects affected / exposed occurrences (all)	6 / 69 (8.70%) 10		
Pain in extremity subjects affected / exposed occurrences (all)	11 / 69 (15.94%) 13		
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	9 / 69 (13.04%) 16		
Device related infection subjects affected / exposed occurrences (all)	5 / 69 (7.25%) 5		
Ear infection subjects affected / exposed occurrences (all)	13 / 69 (18.84%) 18		
Gastroenteritis subjects affected / exposed occurrences (all)	16 / 69 (23.19%) 20		
Gastroenteritis viral subjects affected / exposed occurrences (all)	4 / 69 (5.80%) 5		
Gastrointestinal infection subjects affected / exposed occurrences (all)	4 / 69 (5.80%) 9		
Hand-foot-and-mouth disease subjects affected / exposed occurrences (all)	5 / 69 (7.25%) 5		
Influenza			

subjects affected / exposed	7 / 69 (10.14%)		
occurrences (all)	8		
Nasopharyngitis			
subjects affected / exposed	18 / 69 (26.09%)		
occurrences (all)	52		
Otitis media			
subjects affected / exposed	5 / 69 (7.25%)		
occurrences (all)	5		
Pneumonia			
subjects affected / exposed	7 / 69 (10.14%)		
occurrences (all)	9		
Respiratory tract infection			
subjects affected / exposed	16 / 69 (23.19%)		
occurrences (all)	62		
Rhinitis			
subjects affected / exposed	10 / 69 (14.49%)		
occurrences (all)	17		
Tonsillitis			
subjects affected / exposed	5 / 69 (7.25%)		
occurrences (all)	5		
Upper respiratory tract infection			
subjects affected / exposed	17 / 69 (24.64%)		
occurrences (all)	31		
Urinary tract infection			
subjects affected / exposed	8 / 69 (11.59%)		
occurrences (all)	8		
Viral upper respiratory tract infection			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	4		
Metabolism and nutrition disorders			
Food intolerance			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	5		
Hypocalcaemia			
subjects affected / exposed	6 / 69 (8.70%)		
occurrences (all)	8		

Hypoglycaemia			
subjects affected / exposed	6 / 69 (8.70%)		
occurrences (all)	6		
Hypokalaemia			
subjects affected / exposed	6 / 69 (8.70%)		
occurrences (all)	7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 October 2011	Amendment 1: The major changes to the protocol made with this amendment included the following: <ul style="list-style-type: none">• The duration of the study was extended to 24 months or until regulatory approval for asfotase alfa was obtained.• The BOT-2 was added to the list of clinical assessments and all functional assessments were added to the Month 9 study visit• Change from Baseline in the Gross Motor Milestone Checklist was added as a secondary endpoint
27 October 2011	EU Amendment 1 to German sites. The major changes to the protocol made with this amendment were identical to those made to the USA, Canadian, Taiwanese and Turkish versions under Protocol ENB-010-10 Amendment 1 (13 October 2011), except the duration of the study was extended to 48 months (not 24). Amendment 1 was not submitted for approval.
15 December 2011	EU Amendment 2: There were no new major changes to the protocol with this amendment and it was not submitted or implemented.
06 June 2012	EU Amendment 3: There were no new major changes to the protocol with this amendment and it was not implemented.
10 October 2012	EU Amendment 4: The following major changes were made to the protocol with this amendment: <ul style="list-style-type: none">• Vital signs collection was added following study drug administration.• The schedule originally indicated that skeletal radiographs should be obtained at Month 15, which was incorrect. This mistake was corrected.
25 October 2012	Japan Amendment 1.3: The version of the protocol first implemented at sites in Japan was Version 1.2 dated 09 October 2012. Per the Japanese protocol, patients enrolled were to be hospitalized for the first week of the study, regardless of disease severity. The major changes in the conduct of the study which were made with subsequent versions of the protocol for the sites in Japan are summarized below: Version 1.3 (25 October 2012): <ul style="list-style-type: none">• Enrollment was changed from 3 to 4 patients from Japan• Skeletal radiographs to be obtained at the Month 15 visit were added to the schedule of assessments.
24 January 2013	Amendment 5: The major change to the protocol made with this amendment was to allow for expansion of the study into territories outside of the EU not currently covered under the protocol including Australia, Germany, Italy, Saudi Arabia, Spain, and UK) <ul style="list-style-type: none">• The protocol number was changed from ENB-010-10 (EU-specific) to ENB-010-10• The total number of patients to be enrolled was increased from 30 to 60 patients• The asfotase alfa treatment period was changed to continue until the product becomes registered and available to treat patients diagnosed with HPP (in accordance with country specific regulations), or for a maximum of approximately 48 months, whichever occurred first. In the UK, patient participation may have continued for a maximum of 48 months.

04 March 2013	<p>Japan Amendment 1.4:</p> <ul style="list-style-type: none"> • Total enrollment was changed to up to 5 patients from Japan. • Historical values for vitamin D obtained within 3 months before the Screening visit were allowed to be used to determine patient eligibility. • In Version 1.3 of the protocol, skeletal radiographs obtained at Month 15 were added, which was incorrect. This mistake was corrected.
07 March 2013	<p>Amendment 6 (French-specific)</p> <ul style="list-style-type: none"> • The primary reason for Amendment 6 was to clarify the details of study drug administration for the maximum allowable dose of 9 mg/kg/week, such that study drug would be administered at a dosing regimen of either 1.5 mg/kg 6 times per week or 3 mg/kg 3 times per week.
06 May 2013	<p>Amendment 7(French-specific)</p> <p>Significant changes made to the protocol in Amendment 7, for France, included the following:</p> <ul style="list-style-type: none"> • Considering the age of patients being enrolled in this clinical study (≤ 5 years), the description of assent for study participation was removed as not applicable. • Actual timing for a planned interim statistical analysis was added (after
06 June 2013	<p>Japan Amendment 1.5:</p> <ul style="list-style-type: none"> • The total number of enrollment for the study was revised from 30 to 60 patients, based on the revision of the EU protocol.
27 September 2013	<p>Japan Amendment 1.6: There were no new major changes with this version.</p>
12 March 2014	<p>Japan Amendment 1.7:</p> <ul style="list-style-type: none"> • Procedures for home injection were added to reduce the burden on the patient for site visits as well as a plan to differentiate home versus site injections in the analysis at the onset of any AEs.
02 June 2014	<p>Amendment 8:</p> <p>Global Protocols (Except for Japan) – Not Submitted</p> <p>Protocol Amendment 8 was written to update and harmonize protocol requirements across the aforementioned regions. Significant changes from the regional protocols to Protocol Amendment 8, included the following:</p> <ul style="list-style-type: none"> • Incorporation of relevant changes from Amendment 1 (Canada, Taiwan, Turkey, US), Amendment 5 (Australia, Germany, Italy, Saudi Arabia, Spain, UK, and Amendment 7 (France) to create 1 global protocol (excluding Japan) for use. • Increase in enrollment from approximately 30 (Amendment 1) or 60 (Amendments 5 and 7) patients to approximately 80 patients and the number of sites from approximately 20 to approximately 25. • Extension of the study duration to regulatory approval and commercial availability of asfotase alfa or a maximum of 72 or (in the UK) 48 months.
15 September 2014	<p>Amendment 9:</p> <p>Significant changes made to the protocol in Amendment 9, which was global except for Japan, included the following:</p> <ul style="list-style-type: none"> • Change in wording on the study duration to clarify that the minimum treatment duration for patients will be 12 months, and that the overall study duration will be approximately 72 months, except in the UK where patient participation may continue for a maximum of 48 months. • Change in exclusion criteria regarding bisphosphonates to allow patients who received ≤ 2 cumulative doses of bisphosphonates to enroll in the study, upon approval of Alexion's Medical Monitor.
07 November 2014	<p>Japan Amendment 1.8:</p> <ul style="list-style-type: none"> • The contact information for SAE reporting was revised. • The study period completion date was revised to add an extra 6 months of patient participation, from 31 December 2014 to 30 June 2015.
09 March 2015	<p>Japan Amendment 1.9:</p> <p>Amendment 1.9 was aligned with global protocol ver8.0</p> <p>Global protocol ver. 8.0 was the first integrated international protocol for 10-10 study.</p>

10 April 2015	<p>Amendment 10:</p> <p>Significant changes made to the protocol in Amendment 10, which was global except for Japan, included the following:</p> <ul style="list-style-type: none"> • Clarified the treatment/study duration in anticipation of marketing approval. Protocol text was modified clarifying that patient participation in the study may continue until the product is registered and/or available to treat patients diagnosed with HPP (in accordance with country-specific regulations) or until approximately 72 months (regardless of duration of asfotase alfa treatment for individual patients) (whichever occurs first), except in the UK where patient participation may continue for a maximum of 48 months. Text indicating that patients will receive treatment with asfotase alfa for a minimum of 12 months was removed. • Approximate number of patients to be enrolled was updated from 80 to 100 patients.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None

Notes: