



Clinical trial results:

Extension Study of ENB-0040 (Human Recombinant Tissue-Nonspecific Alkaline Phosphatase Fusion Protein) in Severely Affected Infants and Young Children with Hypophosphatasia (HPP)

Summary

EudraCT number	2009-009369-32
Trial protocol	GB
Global end of trial date	07 February 2017

Results information

Result version number	v1 (current)
This version publication date	17 September 2017
First version publication date	17 September 2017

Trial information

Trial identification

Sponsor protocol code	ENB-003-08
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01205152
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alexion Pharma GmbH
Sponsor organisation address	Giesshübelstrasse 30, Zurich, Switzerland, 8045
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-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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 August 2016
Global end of trial reached?	Yes
Global end of trial date	07 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To determine the long-term tolerability of subcutaneous (SC) Asfotase alfa
- To assess the long-term efficacy of Asfotase alfa in treating rickets in infants and young children with HPP

Protection of trial subjects:

No specific measure

Background therapy: -

Evidence for comparator:

No comparator was used

Actual start date of recruitment	01 April 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	United States: 6
Country: Number of subjects enrolled	United Arab Emirates: 1
Worldwide total number of subjects	10
EEA total number of subjects	3

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	1
Infants and toddlers (28 days-23 months)	6
Children (2-11 years)	3
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0

Subject disposition

Recruitment

Recruitment details:

Criteria for inclusion in Study ENB-002-08 were male and female patients less than or equal to 36 months of age, with severe infantile-onset HPP (symptom onset before 6 months) who were medically stable (ventilator support was allowed). To enter extension Study ENB-003-08, parent/guardian had to consent and patient had to complete Study ENB-002-08.

Pre-assignment

Screening details:

All screened patients met eligibility criteria and were enrolled in the study

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:

All enrolled patients continued on the same dose they were receiving at the end of study ENB-002-08 with adjustments permitted for weight, lack of efficacy, or safety-related concerns.

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:

thrice weekly SC (subcutaneous) injections of Asfotase Alfa

Number of subjects in period 1	Asfotase Alfa
Started	10
Completed	9
Not completed	1
Adverse event, serious fatal	1

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial
Reporting group description:	
Of the 11 patients who were enrolled in Study ENB-002-08, 10 patients completed Study ENB-002-08 and were enrolled in extension study ENB-003-08.	

Reporting group values	Overall Trial	Total	
Number of subjects	10	10	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	1	1	
Infants and toddlers (28 days-23 months)	6	6	
Children (2-11 years)	3	3	
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			
Units: weeks			
arithmetic mean	56.44		
standard deviation	± 61.888	-	
Gender categorical			
Units: Subjects			
Female	6	6	
Male	4	4	
Ethnicity			
Units: Subjects			
Hispanic or Latino	1	1	
Not Hispanic or Latino	9	9	
Race			
Units: Subjects			
White	10	10	

End points

End points reporting groups

Reporting group title	Asfotase Alfa
Reporting group description: All enrolled patients continued on the same dose they were receiving at the end of study ENB-002-08 with adjustments permitted for weight, lack of efficacy, or safety-related concerns.	

Primary: Long-term Tolerability of Subcutaneous (SC) Asfotase Alfa

End point title	Long-term Tolerability of Subcutaneous (SC) Asfotase Alfa ^[1]
End point description: Outcome measure is the number of patients with 1 or more treatment-emergent adverse event. The time period is from Baseline in the ENB-003-08 study to the end of the ENB-003-08 study.	
End point type	Primary
End point timeframe: 84 months	

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	10			
Units: Patients	10			

Statistical analyses

No statistical analyses for this end point

Primary: Long-term Efficacy of Asfotase Alfa in Treating Rickets in Infants and Young Children With HPP

End point title	Long-term Efficacy of Asfotase Alfa in Treating Rickets in Infants and Young Children With HPP ^[2]
End point description: Outcome measure is the evaluation of skeletal radiographs using a qualitative Radiographic Global Impression of Change (RGI-C) Scale, compared with Baseline in Study ENB-002-08 (NCT00744042). The time period is pre-dose (Baseline from ENB-002-08 study) to the last assessment for each patient in the ENB-003-08 study, which represents up to 90 months of exposure for the combined studies.	
End point type	Primary
End point timeframe: 90 months	

Notes:

[2] - 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	10			
Units: units on a scale				
median (full range (min-max))	2 (2 to 3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Long-term Pharmacodynamics (PD) of SC Asfotase Alfa: Plasma Inorganic Pyrophosphate (PPi) Levels

End point title	Long-term Pharmacodynamics (PD) of SC Asfotase Alfa: Plasma Inorganic Pyrophosphate (PPi) Levels
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End point description:

Outcome measure is the change from Baseline in plasma inorganic pyrophosphate (PPi) levels. The time period is pre-dose (Baseline from the ENB-002-08 study [NCT00744042]) to the last assessment for each patient in the ENB-003-08 study, which represents up to 90 months of exposure for the combined studies.

End point type	Secondary
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End point timeframe:

90 months

End point values	Asfotase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	7 ^[3]			
Units: uM				
median (full range (min-max))				
PPi change from baseline (uM)	-2.46 (-9.73 to 2.72)			

Notes:

[3] - Change from Baseline could not be calculated for 3 patients due to non-evaluable samples at Baseline

Statistical analyses

No statistical analyses for this end point

Secondary: To assess the long-term pharmacodynamics (PD) of SC asfotase alfa: Pyridoxal-5-phosphate (PLP) levels

End point title	To assess the long-term pharmacodynamics (PD) of SC asfotase alfa: Pyridoxal-5-phosphate (PLP) levels
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End point description:

Outcome measure is the change from Baseline in pyridoxal-5-phosphate (PLP) levels. The time period is pre-dose (Baseline from the ENB-002-08 study [NCT00744042]) to the last assessment for each patient in the ENB-003-08 study, which represents up to 90 months of exposure for the combined studies.

End point type Secondary

End point timeframe:

Up to 90 months

End point values	Asfotase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	8 ^[4]			
Units: ng/mL				
median (full range (min-max))				
PLP change from baseline (ng/mL)	-266.2 (-844.3 to 184)			

Notes:

[4] - Change from Baseline could not be calculated for 2 patients due to non-evaluable samples at Baseline

Statistical analyses

No statistical analyses for this end point

Secondary: The effect of SC asfotase alfa on growth: Height/length Z-scores

End point title The effect of SC asfotase alfa on growth: Height/length Z-scores

End point description:

Outcome measure is the change from Baseline in Z-scores for height/length. The time period is pre-dose (Baseline from the ENB-002-08 study [NCT00744042]) to the last assessment in the ENB-003-08 study, which represents up to 90 months of exposure in the combined studies.

End point type Secondary

End point timeframe:

Up to 90 months

End point values	Asfotase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: n/a				
median (full range (min-max))				
Change from Baseline in Z-scores for height/length	1.93 (-3.2 to 4.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: To assess the effect of SC asfotase alfa on growth: Weight Z-scores

End point title	To assess the effect of SC asfotase alfa on growth: Weight Z-scores
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End point description:

Outcome measure is the change from Baseline in Z-scores for weight. The time period is pre-dose (Baseline from the ENB-002-08 study [NCT00744042]) to the last assessment in the ENB-003-08 study, which represents up to 90 months of exposure in the combined studies.

End point type	Secondary
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End point timeframe:

Up to 90 months

End point values	Asfotase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: n/a				
median (full range (min-max))				
Weight Z-score change from baseline	2.43 (-2.9 to 5.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: The effect of SC asfotase alfa on respiratory function

End point title	The effect of SC asfotase alfa on respiratory function
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End point description:

Outcome measure is the shift in the proportion of patients requiring respiratory support at their last assessment in Study ENB-003-08 compared with Baseline. The time period is pre-dose (Baseline from the ENB-002-08 study [NCT00744042]) to the last assessment in the ENB-003-08 study, which represents up to 90 months of exposure in the combined studies.

End point type	Secondary
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End point timeframe:

Up to 90 months

End point values	Asfotase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Participants				
No respiratory support	9			
Supplemental oxygen	0			
Continuous positive airway pressure	0			
Mechanical ventilation	1			
Biphasic positive airway pressure	0			
Other	0			

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 ICF through completion of the patient's participation in the study.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

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	9 / 10 (90.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Central venous catheter removal			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tracheal fistula repair			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tracheostomy tube removal			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

General disorders and administration site conditions			
Immediate post-injection reaction			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
medical device complication			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Adenoidal disorder			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Apnoeic attack			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Asthma			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Restrictive pulmonary disease			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sleep apnoea syndrome			

subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tonsillar disorder			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood urea increased			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
CSF pressure			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigation			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Stress fracture			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Congenital bowing of long bones			

subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Craniosynostosis			
subjects affected / exposed	4 / 10 (40.00%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 0		
Talipes			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cyanosis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Intracranial pressure increased			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Conductive deafness			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Papilloedema			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Chronic hepatitis			

subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract obstruction			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Scoliosis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacterial tracheitis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Croup infectious			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			

subjects affected / exposed	3 / 10 (30.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Tracheitis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Feeding disorder of infancy or early childhood			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Weight gain poor			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Asfotase Alfa		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			

subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Skin papilloma subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
General disorders and administration site conditions			
Catheter site rash subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Injection site atrophy subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2		
Injection site calcification subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2		
Injection site discolouration subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Injection site erythema subjects affected / exposed occurrences (all)	4 / 10 (40.00%) 18		
Injection site haematoma subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Injection site hypertrophy subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 8		
Injection site inflammation subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2		
Injection site nodule subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Injection site reaction			

subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 3		
Injection site swelling subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 5		
Injection site warmth subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Pain subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 4		
Pyrexia subjects affected / exposed occurrences (all)	7 / 10 (70.00%) 21		
Vaccination site inflammation subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Immunisation reaction subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Seasonal allergy subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Reproductive system and breast disorders Breast enlargement subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Respiratory, thoracic and mediastinal disorders Adenoidal disorder subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Bronchial hyperreactivity			

subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	6		
Epistaxis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	4		
Increased upper airway secretion			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Nasal congestion			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Nasal polyps			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Rales			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Respiratory distress			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Rhinitis allergic			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	4		
Rhinorrhoea			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	4		
Sinus congestion			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Sleep apnoea syndrome			

subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Tonsillar hypertrophy subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2		
Wheezing subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 5		
Psychiatric disorders			
Abnormal behaviour subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Agitation subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Anticipatory anxiety subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Anxiety subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Fear of needles subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Sleep disorder subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Blood alkaline phosphatase abnormal subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Oxygen saturation decreased			

subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 3		
Staphylococcus test positive subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Vitamin D decreased subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2		
Vitamin D increased subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Hypophosphataemic rickets subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Injury, poisoning and procedural complications			
Adverse event following immunisation subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Arthropod sting subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Clavicle fracture subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2		
Contusion subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Face injury subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Foreign body subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Hand fracture			

subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Head injury			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Joint sprain			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Limb injury			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Lower limb fracture			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Mouth injury			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Periorbital haematoma			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Procedural complication			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Procedural pain			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Procedural site reaction			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Rib fracture			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Scapula fracture			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Skin laceration			

<p>subjects affected / exposed occurrences (all)</p> <p>Tibia fracture subjects affected / exposed occurrences (all)</p> <p>Tracheal haemorrhage subjects affected / exposed occurrences (all)</p> <p>Upper limb fracture subjects affected / exposed occurrences (all)</p> <p>Urine calcium/creatinine ratio increased subjects affected / exposed occurrences (all)</p>	<p>2 / 10 (20.00%) 2</p> <p>2 / 10 (20.00%) 2</p> <p>1 / 10 (10.00%) 1</p> <p>1 / 10 (10.00%) 2</p> <p>2 / 10 (20.00%) 3</p>		
<p>Congenital, familial and genetic disorders Craniosynostosis subjects affected / exposed occurrences (all)</p>	<p>2 / 10 (20.00%) 5</p>		
<p>Nervous system disorders Headache subjects affected / exposed occurrences (all)</p> <p>Speech disorder developmental subjects affected / exposed occurrences (all)</p>	<p>5 / 10 (50.00%) 14</p> <p>2 / 10 (20.00%) 2</p>		
<p>Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)</p> <p>Leukopenia subjects affected / exposed occurrences (all)</p> <p>Microcytosis subjects affected / exposed occurrences (all)</p> <p>Neutropenia</p>	<p>1 / 10 (10.00%) 1</p> <p>1 / 10 (10.00%) 1</p> <p>1 / 10 (10.00%) 1</p>		

subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Eustachian tube dysfunction			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Middle ear disorder			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Otorrhoea			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Tympanic membrane perforation			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Vertigo			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Eye disorders			
Astigmatism			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Conjunctival deposit			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Conjunctival hyperaemia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Conjunctivitis			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	3		
Eye pain			

subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2		
Lacrimation increased subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Myopia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Optic disc drusen subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Optic nerve disorder subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Papilloedema subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Visual impairment subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 4		
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Abdominal pain subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 9		
Constipation subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 4		
Dental caries subjects affected / exposed occurrences (all)	4 / 10 (40.00%) 5		
Diarrhoea subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 5		

Dysphagia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Gastritis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Gingival swelling			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Gingivitis			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Ileus			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Impaired gastric emptying			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Mouth ulceration			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Stomatitis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Teething			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Tooth loss			
subjects affected / exposed	4 / 10 (40.00%)		
occurrences (all)	8		
Toothache			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		

Vomiting subjects affected / exposed occurrences (all)	5 / 10 (50.00%) 14		
Hepatobiliary disorders Cholelithiasis subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Alopecia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Dermatitis allergic subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Dry skin subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Excessive granulation tissue subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Lipohypertrophy subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Rash subjects affected / exposed occurrences (all)	4 / 10 (40.00%) 5		
Rash papular subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 3		
Skin discolouration subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2		
Skin irritation			

subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Urticaria subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Urticaria contact subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Renal and urinary disorders			
Dysuria subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2		
Haematuria subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Hydronephrosis subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 3		
Nephrocalcinosis subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Renal cyst subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2		
Renal pain subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2		
Nephrolithiasis subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Endocrine disorders			
Precocious puberty subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Back pain			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Foot deformity			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Mobility decreased			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Osteopenia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	4 / 10 (40.00%)		
occurrences (all)	19		
Scoliosis			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Infections and infestations			
Abscess jaw			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Acute sinusitis			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	4		
Bronchitis			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Cellulitis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
conjunctivitis infective			

subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Croup infectious			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	3		
Cystitis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	9		
Gastroenteritis viral			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
H1N1 influenza			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Hordeolum			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	7		
Injection site cellulitis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	3		
Laryngitis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Lice infestation			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Lower respiratory tract infection			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Molluscum contagiosum			

subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Otitis externa			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Otitis media			
subjects affected / exposed	6 / 10 (60.00%)		
occurrences (all)	23		
Otitis media acute			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Otitis media chronic			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Pharyngitis			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	8		
Pneumonia			
subjects affected / exposed	5 / 10 (50.00%)		
occurrences (all)	7		
Pneumonia bacterial			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
pneumonia primary atypical			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	5		
Sinusitis			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	8		
Skin infection			

subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Tonsillitis subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 6		
Tooth abscess subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Tracheitis subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 5		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	8 / 10 (80.00%) 77		
Varicella subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Viral infection subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 3		
Viral pharyngitis subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 5		
Metabolism and nutrition disorders			
Abnormal weight gain subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Fluid overload subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Weight gain poor subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 March 2009	The reference to compassionate use has been removed
15 June 2009	<ul style="list-style-type: none">o Increase of the study center and patient enrolled numbero Ventilator use assessment was changed to Respiratory supporto Addition of assessment: PTH, urinary calcium and renal ultrasound
01 February 2010	<ul style="list-style-type: none">o Study duration increase to 2 yearso Addition of several new assessment (i.e dental assessment, fundoscopic examination and vital sign assessment)o Safety section of the protocol was revised to clarify some points
15 February 2011	study duration was increased and included changes to the main inclusion and exclusion criteria
18 April 2011	End of Study was re-defined based on competent authorities feedback
21 February 2012	the main changes were to align the assessment schedule and extend the study period to 60 months
05 December 2013	the main changes were to align the assessment schedule and extend the study period to 84 months or until regulatory approval and commercial availability of asfotase alfa
10 February 2014	<ul style="list-style-type: none">o The maximum study duration for the United Kingdom has been specifically called out as being 84 monthso Contact information for reporting serious adverse events has been added.
11 June 2014	the main changes were to align the assessment schedule
09 February 2015	the main changes was to clarify the fact that medical and surgical history collection for the study includes additional historical information relevant to HPP

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported