Clinical trial results:
Extension Study of Protocol ENB-006-09 Evaluating the Long-Term Safety and Efficacy of Asfotase Alfa (Human Recombinant Tissue-Nonspecific Alkaline Phosphatase Fusion Protein) in Children with Hypophosphatasia (HPP)

Summary

EudraCT number	2017-003153-42
Trial protocol	Outside EU/EEA
Global end of trial date	30 June 2016

Results information

Result version number	v1 (current)
This version publication date	20 October 2018
First version publication date	20 October 2018

Trial information

Trial identification

Sponsor protocol code	ENB-008-10

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01203826
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	30 June 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2016
Global end of trial reached?	Yes
Global end of trial date	30 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study is an extension study of Protocol ENB-006-09. The primary objectives of this study are to assess the long-term tolerability of subcutaneous (SC) asfotase alfa and to assess the proportion of asfotase alfa-treated patients showing radiographic change in rickets severity from the Baseline of Study ENB-006-09 relative to the End of Study (EOS) visit in Study ENB-008-10 using an ordinal Radiographic Global Impression of Change (RGI-C) scale score.

Protection of trial subjects:

This study was designed, conducted, recorded, and reported in accordance with ethical principles that have their origin in the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, and are consistent with International Council on Harmonisation Good Clinical Practice guidelines and in accordance with applicable local, federal, and regulatory agency regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 April 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	Canada: 3
Country: Number of subjects enrolled	United States: 9
Worldwide total number of subjects	12
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	10
Adolescents (12-17 years)	2
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The main criteria for inclusion in Study ENB-006-09 were patients ages 5 to 12 years inclusive, with open growth plates at time of study entry and a documented diagnosis of HPP. To enter the extension, Study ENB-008-10, patients had to successfully complete Study ENB-006-09 and provide consent.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	2 mg/kg Asfotase Alfa

Arm description:

Upon initial enrollment in Study ENB-006-09, patients were randomized to receive 2 milligram (mg)/kilogram (kg) asfotase alfa 3 times weekly. In study ENB-008-010 (extension study of ENB-006-09), patients received a starting dose of 3 mg/kg/week asfotase alfa. The dose in the extension study was subsequently increased per study-wide dose adjustment to a total dose of 6 mg/kg/week. Results are shown by the patient's dose group assignment from Study ENB-006-09. Results presented are for Study ENB-008-10 only.

Arm type	Experimental
Investigational medicinal product name	Asfotase Alfa
Investigational medicinal product code	
Other name	human recombinant tissue nonspecific alkaline phosphatase fusion protein
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

In this extension study, all patients initially received 3 mg/kg/week of asfotase alfa administered by SC injection. Following analysis of results from Study ENB-006-09, the dosage was modified such that patients received 6 mg/kg/week, administered as 2 mg/kg 3 times per week or as 1 mg/kg 6 times per week at the discretion of the Investigator. Patients received treatment with asfotase alfa for at least 72 months or until the product became commercially available.

Arm title	3 mg/kg Asfotase Alfa

Arm description:

Upon initial enrollment in Study ENB-006-09, patients were randomized to receive 3 mg/kg asfotase alfa 3 times weekly. In study ENB-008-010 (extension study of ENB-006-09), patients received a starting dose of 3 mg/kg/week asfotase alfa. The dose in the extension study was subsequently increased per study-wide dose adjustment to a total dose of 6 mg/kg/week. Results are shown by the patient's dose group assignment from Study ENB-006-09. Results presented are for Study ENB-008-10 only.

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patients received 6 mg/kg/week, administered as 2 mg/kg 3 times per week or as 1 mg/kg 6 times per week at the discretion of the Investigator. Patients received treatment with asfotase alfa for at least 72 months or until the product became commercially available.

Number of subjects in period 1	2 mg/kg Asfotase Alfa	3 mg/kg Asfotase Alfa
Started	6	6
Completed	6	6

Baseline characteristics

Reporting groups	
Reporting group title	2 mg/kg Asfotase Alfa
Reporting group description:	
Upon initial enrollment in Study ENB-006-09, patients were randomized to receive 2 milligram (mg)/kilogram (kg) asfotase alfa 3 times weekly. In study ENB-008-010 (extension study of ENB-006-09), patients received a starting dose of 3 mg/kg/week asfotase alfa. The dose in the extension study was subsequently increased per study-wide dose adjustment to a total dose of 6 mg/kg/week. Results are shown by the patient's dose group assignment from Study ENB-006-09. Results presented are for Study ENB-008-10 only.	
Reporting group title	3 mg/kg Asfotase Alfa
Reporting group description:	
Upon initial enrollment in Study ENB-006-09, patients were randomized to receive 3 mg/kg asfotase alfa 3 times weekly. In study ENB-008-010 (extension study of ENB-006-09), patients received a starting dose of 3 mg/kg/week asfotase alfa. The dose in the extension study was subsequently increased per study-wide dose adjustment to a total dose of 6 mg/kg/week. Results are shown by the patient's dose group assignment from Study ENB-006-09. Results presented are for Study ENB-008-10 only.	

Reporting group values	2 mg/kg Asfotase Alfa	3 mg/kg Asfotase Alfa	Total
Number of subjects	6	6	12
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	5	5	10
Adolescents (12-17 years)	1	1	2
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
median	8.4	9.0	
standard deviation	± 2.21	± 2.51	-
Gender categorical Units: Subjects			
Female	1	1	2
Male	5	5	10
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	6	6	12
More than one race	0	0	0
Unknown or Not Reported	0	0	0

Ethnicity Units: Subjects			
Hispanic or Latino	1	0	1
Not Hispanic or Latino	5	6	11
Unknown or Not Reported	0	0	0
Region of Enrollment Units: Subjects			
Canada	2	1	3
United States	4	5	9
Hypophosphatasia Phenotype Units: Subjects			
Infantile (< 6 months)	3	1	4
Juvenile (≥ 6 months to < 18 yrs)	3	5	8
Tanner Staging			
Measure Description: n %; Tanner Stage 1 = Prepubertal children			
Units: Subjects			
Tanner Stage 1	6	6	12
Age at Onset of Hypophosphatasia Symptoms Units: Months			
arithmetic mean	10.8	11.5	
standard deviation	± 8.66	± 5.54	-

Subject analysis sets

Subject analysis set title	Asfotase Alfa Combined
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All patients that received treatment with asfotase alfa in Study ENB-008-10.

Reporting group values	Asfotase Alfa Combined		
Number of subjects	12		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	10		
Adolescents (12-17 years)	2		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
median	8.7		
standard deviation	± 2.27		
Gender categorical Units: Subjects			
Female	2		

Male	10		

Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	0		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	0		
White	12		
More than one race	0		
Unknown or Not Reported	0		
Ethnicity Units: Subjects			
Hispanic or Latino	1		
Not Hispanic or Latino	11		
Unknown or Not Reported	0		
Region of Enrollment Units: Subjects			
Canada	3		
United States	9		
Hypophosphatasia Phenotype Units: Subjects			
Infantile (< 6 months)	4		
Juvenile (≥ 6 months to < 18 yrs)	8		
Tanner Staging			
Measure Description: n %; Tanner Stage 1 = Prepubertal children			
Units: Subjects			
Tanner Stage 1	12		
Age at Onset of Hypophosphatasia Symptoms Units: Months			
arithmetic mean	11.2		
standard deviation	± 6.94		

End points

End points reporting groups

Reporting group title	2 mg/kg Asfotase Alfa

Reporting group description:

Upon initial enrollment in Study ENB-006-09, patients were randomized to receive 2 milligram (mg)/kilogram (kg) asfotase alfa 3 times weekly. In study ENB-008-010 (extension study of ENB-006-09), patients received a starting dose of 3 mg/kg/week asfotase alfa. The dose in the extension study was subsequently increased per study-wide dose adjustment to a total dose of 6 mg/kg/week. Results are shown by the patient's dose group assignment from Study ENB-006-09. Results presented are for Study ENB-008-10 only.

Reporting group title	3 mg/kg Asfotase Alfa

Reporting group description:

Upon initial enrollment in Study ENB-006-09, patients were randomized to receive 3 mg/kg asfotase alfa 3 times weekly. In study ENB-008-010 (extension study of ENB-006-09), patients received a starting dose of 3 mg/kg/week asfotase alfa. The dose in the extension study was subsequently increased per study-wide dose adjustment to a total dose of 6 mg/kg/week. Results are shown by the patient's dose group assignment from Study ENB-006-09. Results presented are for Study ENB-008-10 only.

Subject analysis set title	Asfotase Alfa Combined
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All patients that received treatment with asfotase alfa in Study ENB-008-10.

Primary: Skeletal Radiograph Evaluation Using a Qualitative RGI-C Scale Compared to Baseline (Pre-treatment) in Study ENB-006-09

End point title	Skeletal Radiograph Evaluation Using a Qualitative RGI-C Scale Compared to Baseline (Pre-treatment) in Study ENB-006-09[1]

End point description:

Evaluation of radiographic change in rickets severity (assessed by skeletal radiographs of hands/wrists and knees) from Baseline of Study ENB-006-09 (EudraCT number 2015-001128-52, NCT00952484) to EOS visit in Study ENB-008-10 using an ordinal RGI-C scale score. The RGI-C is a 7-point rating scale ranging from -3 (indicates severe worsening of HPP associated rickets) to +3 (indicates complete or near complete healing of HPP associated rickets). The timepoints are pre-treatment (Baseline from Study ENB-006-09) to the last radiographic assessment in Study ENB-008-10, which represents at least 72 months of treatment. The RGI-C score represents evaluations of skeletal X-rays at each post-treatment timepoint in Study ENB-008-10 compared with pre-treatment X-rays from Study ENB-006-09, using an ordinal scale. Therefore, no Baseline data for RGI-C are available. A Wilcoxon signed-rank test was used to test if the change in rickets severity was different from 0; the resulting p-value=0.0005.

End point type	Primary

End point timeframe:

At least 72 months of treatment with asfotase alfa

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: Due to the limitations of the EudraCT database, the method used for the calculation of the p-value and the p-value were reported in the endpoint description.

End point values	Asfotase Alfa Combined			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: Units on a Scale				
median (full range (min-max))	2.83 (2.0 to 3.0)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events are events starting on or after the day of first dose of asfotase alfa and recorded in Study ENB-008-10 (at least 66 months of treatment in Study ENB-008-10).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	2 mg/kg Asfotase Alfa

Reporting group description:

Upon initial enrollment in Study ENB-006-09, patients were randomized to receive 2 mg/kg asfotase alfa 3 times weekly. In study ENB-008-010 (extension study of ENB-006- 09), patients received a starting dose of 3 mg/kg/week asfotase alfa. The dose in the extension study was subsequently increased per study-wide dose adjustment to a total dose of 6 mg/kg/week. Results are shown by the patient's dose group assignment from Study ENB-006-09. Results presented are for Study ENB-008-10 only.

Reporting group title	3 mg/kg Asfotase Alfa

Reporting group description:

Upon initial enrollment in Study ENB-006-09, patients were randomized to receive 3 mg/kg asfotase alfa 3 times weekly. In study ENB-008-010 (extension study of ENB-006- 09), patients received a starting dose of 3 mg/kg/week asfotase alfa. The dose in the extension study was subsequently increased per study-wide dose adjustment to a total dose of 6 mg/kg/week. Results are shown by the patient's dose group assignment from Study ENB-006-09. Results presented are for Study ENB-008-10 only.

Reporting group title	Asfotase Alfa Combined

Reporting group description:

All patients that received treatment with asfotase alfa in Study ENB-008-10.

Serious adverse events	2 mg/kg Asfotase Alfa	3 mg/kg Asfotase Alfa	Asfotase Alfa Combined
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

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

Non-serious adverse events	2 mg/kg Asfotase Alfa	3 mg/kg Asfotase Alfa	Asfotase Alfa Combined
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	6 / 6 (100.00%)	12 / 12 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Haemangioma			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Melanocytic naevus			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	3	0	3
Skin papilloma			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	3 / 12 (25.00%)
occurrences (all)	7	1	8
General disorders and administration site conditions			
Discomfort			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Fatigue			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	3 / 12 (25.00%)
occurrences (all)	2	2	4
Gait disturbance			
subjects affected / exposed	0 / 6 (0.00%)	3 / 6 (50.00%)	3 / 12 (25.00%)
occurrences (all)	0	3	3
Injection site atrophy			
subjects affected / exposed	3 / 6 (50.00%)	3 / 6 (50.00%)	6 / 12 (50.00%)
occurrences (all)	10	8	18
Injection site discolouration			
subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)	4 / 12 (33.33%)
occurrences (all)	8	8	16
Injection site erythema			
subjects affected / exposed	4 / 6 (66.67%)	6 / 6 (100.00%)	10 / 12 (83.33%)
occurrences (all)	18	27	45
Injection site hypersensitivity			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Injection site hypertrophy			
subjects affected / exposed	4 / 6 (66.67%)	4 / 6 (66.67%)	8 / 12 (66.67%)
occurrences (all)	14	13	27
Injection site induration			

subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Injection site macule			
subjects affected / exposed	4 / 6 (66.67%)	5 / 6 (83.33%)	9 / 12 (75.00%)
occurrences (all)	28	31	59
Injection site pain			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	3 / 12 (25.00%)
occurrences (all)	6	2	8
Injection site papule			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Injection site pruritus			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	2 / 12 (16.67%)
occurrences (all)	12	0	12
Injection site reaction			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Injection site swelling			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 12 (8.33%)
occurrences (all)	0	7	7
Injection site urticaria			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Pyrexia			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	3 / 12 (25.00%)
occurrences (all)	2	1	3
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Seasonal allergy			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	7	0	7
Reproductive system and breast disorders			

Balanitis			
subjects affected / exposed[1]	1 / 5 (20.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Respiratory, thoracic and mediastinal disorders			
Allergic cough			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Allergic sinusitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	2	0	2
Cough			
subjects affected / exposed	3 / 6 (50.00%)	0 / 6 (0.00%)	3 / 12 (25.00%)
occurrences (all)	5	0	5
Epistaxis			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	2 / 12 (16.67%)
occurrences (all)	1	1	2
Nasal congestion			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	2	0	2
Oropharyngeal pain			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	2 / 12 (16.67%)
occurrences (all)	1	1	2
Rhinitis allergic			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	2 / 12 (16.67%)
occurrences (all)	1	1	2
Psychiatric disorders			
Acute stress disorder			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Anxiety			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 12 (8.33%)
occurrences (all)	0	2	2
Attention deficit/hyperactivity disorder			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Initial insomnia			

subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Investigations			
Blood 25-hydroxycholecalciferol decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Injury, poisoning and procedural complications			
Accidental exposure			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 12 (8.33%)
occurrences (all)	0	2	2
Ankle fracture			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Arthropod bite			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	2 / 12 (16.67%)
occurrences (all)	2	0	2
Arthropod sting			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Burns second degree			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Contusion			
subjects affected / exposed	3 / 6 (50.00%)	0 / 6 (0.00%)	3 / 12 (25.00%)
occurrences (all)	3	0	3
Drug administration error			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Joint injury			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Joint sprain			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	3 / 12 (25.00%)
occurrences (all)	1	2	3
Limb injury			

subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	2 / 12 (16.67%)
occurrences (all)	1	1	2
Muscle strain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Periorbital haematoma			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Post-traumatic pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Procedural pain			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	2 / 12 (16.67%)
occurrences (all)	3	0	3
Radius fracture			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Testicular injury			
subjects affected / exposed[2]	1 / 5 (20.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed[3]	1 / 5 (20.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Headache			
subjects affected / exposed	3 / 6 (50.00%)	3 / 6 (50.00%)	6 / 12 (50.00%)
occurrences (all)	15	4	19
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Ear and labyrinth disorders			

Ear pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Middle ear inflammation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Eye disorders			
Conjunctival deposit			
subjects affected / exposed	3 / 6 (50.00%)	3 / 6 (50.00%)	6 / 12 (50.00%)
occurrences (all)	5	3	8
Conjunctivitis			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	2 / 12 (16.67%)
occurrences (all)	1	1	2
Conjunctivitis allergic			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Corneal deposits			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Optic atrophy			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Optic disc drusen			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Retinal vascular disorder			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Gastrointestinal disorders			
Dental discomfort			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	3	0	3
Diarrhoea			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	2 / 12 (16.67%)
occurrences (all)	2	0	2
Food poisoning			

subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	2 / 12 (16.67%)
occurrences (all)	0	3	3
Oral pain			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	2 / 12 (16.67%)
occurrences (all)	3	1	4
Tooth crowding			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Toothache			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Vomiting			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	2 / 12 (16.67%)
occurrences (all)	0	2	2
Dermatitis allergic			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Eczema			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	2 / 12 (16.67%)
occurrences (all)	0	2	2
Hair colour changes			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Ingrowing nail			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	2 / 12 (16.67%)
occurrences (all)	0	2	2
Skin discolouration			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1

Urticaria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	2 / 12 (16.67%)
occurrences (all)	0	6	6
Nephrocalcinosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Endocrine disorders			
Growth hormone deficiency			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 6 (66.67%)	1 / 6 (16.67%)	5 / 12 (41.67%)
occurrences (all)	6	2	8
Epiphyses premature fusion			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	2	0	2
Joint hyperextension			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Joint swelling			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	2 / 12 (16.67%)
occurrences (all)	1	2	3
Muscular weakness			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	2 / 12 (16.67%)
occurrences (all)	0	2	2
Musculoskeletal stiffness			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	2	0	2
Myalgia			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	3 / 12 (25.00%)
occurrences (all)	3	1	4

Neck pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Pain in extremity			
subjects affected / exposed	3 / 6 (50.00%)	0 / 6 (0.00%)	3 / 12 (25.00%)
occurrences (all)	6	0	6
Tendonitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	2 / 12 (16.67%)
occurrences (all)	1	2	3
Ear infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Enterobiasis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Gastroenteritis			
subjects affected / exposed	2 / 6 (33.33%)	3 / 6 (50.00%)	5 / 12 (41.67%)
occurrences (all)	3	5	8
Gastroenteritis viral			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	2 / 12 (16.67%)
occurrences (all)	2	0	2
Influenza			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	2	0	2
Otitis media			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Pharyngitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Pharyngitis streptococcal			

subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 12 (8.33%)
occurrences (all)	0	2	2
Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	3 / 6 (50.00%)	3 / 12 (25.00%)
occurrences (all)	0	3	3
Sinusitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	2	0	2
Staphylococcal skin infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 12 (8.33%)
occurrences (all)	0	2	2
Tinea cruris			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Tonsillitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Upper respiratory tract infection			
subjects affected / exposed	5 / 6 (83.33%)	4 / 6 (66.67%)	9 / 12 (75.00%)
occurrences (all)	24	20	44
Viral infection			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	2 / 12 (16.67%)
occurrences (all)	1	2	3

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This adverse event only affects male patients; therefore, only male patients were reported for this event.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This adverse event only affects male patients; therefore, only male patients were reported for this event.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This adverse event only affects male patients; therefore, only male patients were reported for this event.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 May 2010	• Language was added to the description of medical history assessment to collect detailed historical information in the absence of treatment for consenting patients through retrospective medical records review • Language was added to include summarization and analysis of collected medical history • Injection site reactions were included in preliminary safety-related findings for precursor Study ENB-006-09
05 August 2010	• Several functional assessments were added to the Month 3 and 9 study visits to monitor changes in motor function and other measures, including 6-Minute Walk Test (6MWT), shuttle run and standing long jump subtest of the Bruininks-Oseretsky Test of Motor Proficiency, Second Edition (BOT-2), hand-held dynamometry (HHD), and pain portion of the Child Health Assessment Questionnaire (CHAQ) • Language was removed to reflect that adjudication of differing RGI-C scores was not required for statistical analysis of the primary efficacy endpoint for the study
13 October 2010	• Language was added to clarify the primary efficacy endpoint • A single transiliac crest bone biopsy at Month 9 or 12 was added to examination criteria to assist in evaluating the long-term effects of asfotase alfa treatment on osteomalacia when compared with results from the precursor study ENB-006-09 • Additional testing added at Months 3 and 9 for BOT-2 subtests, HHD, and CHAQ disability and pain
01 February 2011	• The study methodology and statistical analyses were updated to reflect that the study was extended from 12 to at least 42 months • The primary objectives of the study were updated to emphasize the long-term tolerability of SC asfotase alfa and the long-term efficacy of asfotase alfa in treating rickets in children with HPP • Secondary and exploratory study objectives were updated to reflect that the study will now focus on the pharmacokinetics of SC asfotase alfa. • The transiliac crest bone biopsy, panorex radiographs, and pulmonary function tests were eliminated. • Examination criteria, including body mass index, arm span, dual energy X-ray absorptiometry, disability, and pain, were changed from exploratory to secondary objectives. • The dose was changed from 3 to 6 mg/kg/week to reflect the interim study results for Study ENB-006-09. • The number of study sites was decreased from 5 to 2 to reflect that only 2 sites had patients enrolled, and the number of patients planned for this study was updated based on the number (12) that completed the initial study. • The dose adjustment language was updated to reflect the fact that safety issues can arise at any time, and it is in the patients' best interest to have flexibility to adjust the dose at any time during the study with input from the Investigator. • The Efficacy Evaluation section was updated to reflect current examination criteria. • Urine calcium:creatinine ratios were moved from safety measures to pharmacodynamic assessments to align with other recent protocols in the program. • X-ray of the lateral skull was removed due to being considered unnecessary as a safety measurement in this population.

30 July 2014	• Extended the study duration to regulatory approval and commercial availability of asfotase alfa or at least 72 months. • Added a requirement for pregnancy testing, as patients in the study were reaching childbearing potential. • Updated wording regarding dose adjustments for efficacy or safety reasons. • Full ophthalmology examinations (including funduscopy) were added to better characterize potential ectopic calcifications. • Changes to Data Monitoring Committee (DMC) operations (endorsed by the DMC) were made based on a new DMC charter (dated 10 Jan 2013) and Sponsor discussions on DMC stopping rules; ad hoc review and stopping rules are no longer required; however, the DMC was to be notified immediately. • Changed testing requirements for injection-associated reactions.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27699270