# 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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Dosage and administration details:

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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<br>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<br>Units: years | | | |
| median | 8.4 | 9.0 | |
| standard deviation | ± 2.21 | ± 2.51 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 1 | 1 | 2 |
| Male | 5 | 5 | 10 |
| Race (NIH/OMB)<br>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<br>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<br>Units: Subjects | | | |
| Canada | 2 | 1 | 3 |
| United States | 4 | 5 | 9 |
| Hypophosphatasia Phenotype<br>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<br>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<br>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<br>Units: years | | | |
| median | 8.7 | | |
| standard deviation | ± 2.27 | | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 2 | | |

| | | | |
|---|---|---|---|
| Male | 10 | | |

| | | | |
|---|---|---|---|
| Race (NIH/OMB)<br>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<br>Units: Subjects | | | |
| Hispanic or Latino | 1 | | |
| Not Hispanic or Latino | 11 | | |
| Unknown or Not Reported | 0 | | |
| Region of Enrollment<br>Units: Subjects | | | |
| Canada | 3 | | |
| United States | 9 | | |
| Hypophosphatasia Phenotype<br>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<br>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<br>• Language was added to include summarization and analysis of collected medical history<br>• 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)<br>• 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<br>• 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<br>• 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<br>• 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<br>• Secondary and exploratory study objectives were updated to reflect that the study will now focus on the pharmacokinetics of SC asfotase alfa.<br>• The transiliac crest bone biopsy, panorex radiographs, and pulmonary function tests were eliminated.<br>• Examination criteria, including body mass index, arm span, dual energy X-ray absorptiometry, disability, and pain, were changed from exploratory to secondary objectives.<br>• The dose was changed from 3 to 6 mg/kg/week to reflect the interim study results for Study ENB-006-09.<br>• 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.<br>• 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.<br>• The Efficacy Evaluation section was updated to reflect current examination criteria.<br>• Urine calcium:creatinine ratios were moved from safety measures to pharmacodynamic assessments to align with other recent protocols in the program.<br>• 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.<br>• Added a requirement for pregnancy testing, as patients in the study were reaching childbearing potential.<br>• Updated wording regarding dose adjustments for efficacy or safety reasons.<br>• Full ophthalmology examinations (including funduscopy) were added to better characterize potential ectopic calcifications.<br>• 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.<br>• 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