Clinical trial results:
A Multicenter, Open-Label Study of the Safety, Tolerability and Pharmacology of Asfotase Alfa in up to 10 Severely Affected Patients With for the Treatment of Severely Affected Patients With Infantile Hypophosphatasia (HPP)

Summary

EudraCT number	2008-007406-11
Trial protocol	GB
Global end of trial date	21 May 2010

Results information

Result version number	v1 (current)
This version publication date	07 August 2016
First version publication date	07 August 2016

Trial information

Trial identification

Sponsor protocol code	ENB-002-08

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00744042
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alexion Pharma GmbH
Sponsor organisation address	Giesshübelstrasse 30, Zurich, Switzerland, 8050
Public contact	Alexion Europe SAS, European Clinical Trial Information, +33 147100606, Clinicaltrials.eu@alxn.com
Scientific contact	Alexion Europe SAS, European Clinical Trial Information, +33 147100606, Clinicaltrials.eu@alxn.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	16 November 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 May 2010
Global end of trial reached?	Yes
Global end of trial date	21 May 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. To assess the efficacy of asfotase alfa in treating the skeletal manifestations of infantile HPP
2. To determine the safety and tolerability of asfotase alfa given intravenously (IV) in a single dose and subcutaneously (SC) in repeat doses

Protection of trial subjects:

No specific measure

Background therapy: -

Evidence for comparator:

No comparator was used in the study

Actual start date of recruitment	06 October 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety, Ethical reason
Long term follow-up duration	7 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 7
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	United Arab Emirates: 1
Country: Number of subjects enrolled	United Kingdom: 2
Worldwide total number of subjects	11
EEA total number of subjects	2

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)	7
Children (2-11 years)	3

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

Subject disposition

Recruitment

Recruitment details:

The trial was posted on clinicaltrials.gov. Physicians managing the care of infants and young children with a confirmed diagnosis of HPP contacted existing sites or requested assistance with site set up from the sponsor

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

Arms

Arm title	Asfotase Alfa

Arm description:

All enrolled patients receive a single IV (intravenous) dose of Asfotase Alfa of 2 mg/kg followed by 7 days of observation. Following an assessment of safety data by an independent Data Safety Monitoring Board (DSMB), patients begin thrice weekly SC (subcutaneous) injections of Asfotase Alfa at a dose of 1 mg/kg for the remaining 23 weeks of the study.

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

Dosage and administration details:

All enrolled patients receive a single IV (intravenous) dose of Asfotase Alfa of 2 mg/kg followed by 7 days of observation. Following an assessment of safety data by an independent Data Safety Monitoring Board (DSMB), patients begin thrice weekly SC (subcutaneous) injections of Asfotase Alfa at a dose of 1 mg/kg for the remaining 23 weeks of the study.

Number of subjects in period 1	Asfotase Alfa
Started	11
Completed	10
Not completed	1
Consent withdrawn by subject	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	11	11	
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)	7	7	
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: years			
arithmetic mean	1.11		
standard deviation	± 1.13	-	
Gender categorical Units: Subjects			
Female	7	7	
Male	4	4	

End points

End points reporting groups

Reporting group title	Asfotase Alfa

Reporting group description:

All enrolled patients receive a single IV (intravenous) dose of Asfotase Alfa of 2 mg/kg followed by 7 days of observation. Following an assessment of safety data by an independent Data Safety Monitoring Board (DSMB), patients begin thrice weekly SC (subcutaneous) injections of Asfotase Alfa at a dose of 1 mg/kg for the remaining 23 weeks of the study.

Primary: Change in Rickets Severity From Baseline to Week 24, Based on Assessment of Skeletal Radiographs Using Radiologic Global Impression of Change (RGI-C)

End point title	Change in Rickets Severity From Baseline to Week 24, Based on Assessment of Skeletal Radiographs Using Radiologic Global Impression of Change (RGI-C)[1]

End point description:

A 7-point RGI-C (Radiographic Global Impression of Change) score was used to rate change in rickets severity. Scores ranged from -3 (severe worsening of rickets) to +3 (complete healing of rickets). Only those patients with a minimum score of +2 indicating substantial healing of rickets) were considered "responders". Three pediatric radiologists not affiliated with the conduct of the study performed the ratings. Average scores were derived for each patient at each assessment.

End point type	Primary

End point timeframe:

24 weeks

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	11[2]			
Units: Units on a scale				
median (full range (min-max))	2 (0 to 2.33)			

Notes:

[2] - ITT (intention to treat)

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Serum Concentration of Asfotase Alfa (Cmax)

End point title	Maximum Serum Concentration of Asfotase Alfa (Cmax)

End point description:

Maximum serum concentration observed during intensive PK sampling interval.

Study Week 1 Intravenous Dose (2 mg/kg Single Dose): Participants received intravenous (IV) asfotase alfa (2 mg/kg single dose) on Day 1. PK samples drawn pre-dose to 168 hours post-dose.
Study Week 2 Subcutaneous Dose (1 mg/kg 3x/Week): Participants received subcutaneous (SC) asfotase alfa starting on Day 8 (Week 2) (1 mg/kg 3x/week). PK samples drawn pre-dose to 48 hours post-dose for PK analysis following single SC dose.

Study Week 3 Subcutaneous Dose (1mg/kg 3x/Week): Participants received subcutaneous (SC) asfotase alfa starting on Day 8 (Week 2) (1 mg/kg 3x/week). PK samples drawn pre-dose to 48 hours post-dose for PK analysis following multiple SC doses.

End point type	Secondary

End point timeframe:

Study Week 1 (0 to 168 hours post-dose). Study Week 2 and Study Week 3 (0 to 48 hours post-dose)

End point values	Asfotase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	11[3]			
Units: U/L				
arithmetic mean (standard deviation)				
Study week 1, IV 2 mg/kg single dose	2230 (± 1100)			
Study week 2, SC 1 mg/kg three times/week	376 (± 226)			
Study week 3, SC 1 mg/kg three times/week	897 (± 491)			

Notes:

[3] - week 1 - 6 participants analysed
week 2 - 7 participants analysed
week 3 - 7 participants analysed

Statistical analyses

No statistical analyses for this end point

Secondary: Time at Maximum Serum Concentration of Asfotase Alfa (Tmax)

End point title	Time at Maximum Serum Concentration of Asfotase Alfa (Tmax)

End point description:

Time at maximum serum concentration observed during intensive PK sampling interval.

Study Week 1 Intravenous Dose (2 mg/kg Single Dose): Participants received intravenous (IV) asfotase alfa (2 mg/kg single dose) on Day 1. PK samples drawn pre-dose to 168 hours post-dose.
Study Week 2 Subcutaneous Dose (1 mg/kg 3x/Week): Participants received subcutaneous (SC) asfotase alfa starting on Day 8 (Week 2) (1 mg/kg 3x/week). PK samples drawn pre-dose to 48 hours post-dose for PK analysis following single SC dose.
Study Week 3 Subcutaneous Dose (1mg/kg 3x/Week): Participants received subcutaneous (SC) asfotase alfa starting on Day 8 (Week 2) (1 mg/kg 3x/week). PK samples drawn pre-dose to 48 hours post-dose for PK analysis following multiple SC doses.

End point type	Secondary

End point timeframe:

Study Week 1 (0 to 168 hours post-dose). Study Week 2 and Study Week 3 (0 to 48 hours post-dose).

End point values	Asfotase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	11[4]			
Units: hour				
arithmetic mean (standard deviation)				
Study week 1 (IV, single dose 2 mg/kg)	4.3 (± 4.3)			

Study week 2 (SC, 1 mg/kg 3 times/week)	29.7 (± 13.2)			
Study week 3 (SC, 1 mg/kg 3 times/week)	12 (± 7.7)			

Notes:

[4] - week 1 - 6 participants analysed
week 2 - 7 participants analysed
week 3 - 7 participants analysed

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under Serum Concentration-time Curve to Last Measurable Concentration of Asfotase Alfa (AUCt)

End point title	Area Under Serum Concentration-time Curve to Last Measurable Concentration of Asfotase Alfa (AUCt)

End point description:

Area under serum concentration-time curve to last measurable concentration during intensive PK sampling interval.

Study Week 1 Intravenous Dose (2mg/kg Single Dose): Participants received intravenous (IV) asfotase alfa (2mg/mg single dose) on Day 1. PK samples drawn pre-dose to 168 hours post-dose.
Study Week 2 Subcutaneous Dose: (1mg/kg 3x/Week) Participants received subcutaneous (SC) asfotase alfa starting on Day 8 (Week 2) (1 mg/kg 3x/week). PK samples drawn pre-dose to 48 hours post-dose for PK analysis following single SC dose.
Study Week 3 Subcutaneous Dose: (1mg/kg 3x/Week) Participants received subcutaneous (SC) asfotase alfa starting on Day 8 (Week 2) (1 mg/kg 3x/week). PK samples drawn pre-dose to 48 hours post-dose for PK analysis following multiple SC doses.

End point type	Secondary

End point timeframe:

Study Week 1 (0 to 168 hours post-dose). Study Week 2 and Study Week 3 (0 to 48 hours post-dose).

End point values	Asfotase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	11[5]			
Units: h*U/L				
arithmetic mean (standard deviation)				
Study week 1 (IV, 2 mg/kg single dose)	79800 (± 21700)			
Study week 2 (SC, 1 mg/kg 3 times/week)	14799 (± 9730)			
Study week 3 (SC, 1 mg/kg 3 times/week)	33700 (± 19700)			

Notes:

[5] - week 1 - 6 participants analysed
week 2 - 7 participants analysed
week 3 - 7 participants analysed

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

6 months

Adverse event reporting additional description:

All patients who received any asfotase alfa treatment, regardless of whether they were lost to follow-up or dropped out of the trial.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13

Reporting groups

Reporting group title	Asfotase Alfa

Reporting group description:

All enrolled patients receive a single IV (intravenous) dose of Asfotase Alfa of 2 mg/kg followed by 7 days of observation. Following an assessment of safety data by an independent Data Safety Monitoring Board (DSMB), patients begin thrice weekly SC (subcutaneous) injections of Asfotase Alfa at a dose of 1 mg/kg for the remaining 23 weeks of the study.

Serious adverse events	Asfotase Alfa		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 11 (63.64%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Oxygen saturation decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Collapse of lung			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
convulsion			
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 11 (18.18%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Intracranial pressure increased				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Medical device related complication	Additional description: Catheter related complication			
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Respiratory distress				
alternative assessment type: Non-systematic				
subjects affected / exposed	2 / 11 (18.18%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
alternative assessment type: Non-systematic				
subjects affected / exposed	2 / 11 (18.18%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Obstructive airway disorder				
alternative assessment type: Non-systematic				

subjects affected / exposed	1 / 11 (9.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Restrictive pulmonary disease				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory depression				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Craniosynostosis				
alternative assessment type: Non-systematic				
subjects affected / exposed	3 / 11 (27.27%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Pneumonia				
alternative assessment type: Non-systematic				
subjects affected / exposed	2 / 11 (18.18%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis salmonella				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection viral				
alternative assessment type: Non-systematic				

subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia respiratory syncytial viral			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory syncytial virus bronchiolitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
H1N1 influenza1 Influenza			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Asfotase Alfa		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 11 (100.00%)		
Vascular disorders			
Flushing			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Secondary hypertension			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Surgical and medical procedures			
Central venous catheter removal			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
General disorders and administration site conditions			
Pyrexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 11 (45.45%)		
occurrences (all)	5		
Irritability			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 11 (36.36%)		
occurrences (all)	4		
Injection site erythema			

alternative assessment type: Non-systematic				
subjects affected / exposed	2 / 11 (18.18%)			
occurrences (all)	15			
Catheter site erythema				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Catheter site rash				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Thrombosis in device				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Chills				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Drug withdrawal syndrome				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Hernia				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Injection site haematoma				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	4			
Injection site induration				
alternative assessment type: Non-systematic				

subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	2			
Injection site nodule				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	2			
Injection site pain				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Injection site papule				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Injection site pruritus				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	2			
Injection site rash				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	2			
Injection site warmth				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	2			
Oedema				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Pain				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			

Immune system disorders			
Seasonal allergy			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Nasal ulcer			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Tachypnoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Pharyngeal erythema			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Respiratory depression			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Psychiatric disorders			
Drug dependence			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	3		
Agitation			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		

Breath holding			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Anxiety			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Investigations			
Haemoglobin decreased			
subjects affected / exposed	4 / 11 (36.36%)		
occurrences (all)	9		
Urine calcium/creatinine ratio increased			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Culture positive			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Fall			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Procedural pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Procedural site reaction			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Radius fracture			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Wound			

alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Feeding tube complication			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Congenital, familial and genetic disorders			
Congenital bowing of long bones			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Craniosynostosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Atrial septal defect			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Cardiac disorders			
Bradycardia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Anemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Tachycardia			

alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Eye disorders			
Ocular hyperaemia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Gastrointestinal disorders			
Vomiting			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	3		
Constipation			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 11 (36.36%)		
occurrences (all)	4		
Flatulence			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Gastrooesophageal reflux disease			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Gingival erythema			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Stomatitis			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Teething			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Hypothermia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Diarrhea			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Gastritis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Dermatitis diaper			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Erythema			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Excessive granulation tissue			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Hyperhidrosis			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Increased tendency to bruise			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	6		
Piloerection			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Renal and urinary disorders			
Nephrolithiasis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Bone pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Myalgia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Pain in extremity			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Infections and infestations			
Pneumonia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		

Nasopharyngitis				
alternative assessment type: Non-systematic				
subjects affected / exposed	2 / 11 (18.18%)			
occurrences (all)	4			
Otitis media				
alternative assessment type: Non-systematic				
subjects affected / exposed	2 / 11 (18.18%)			
occurrences (all)	2			
Sinusitis				
alternative assessment type: Non-systematic				
subjects affected / exposed	2 / 11 (18.18%)			
occurrences (all)	3			
Upper respiratory tract infection				
alternative assessment type: Non-systematic				
subjects affected / exposed	2 / 11 (18.18%)			
occurrences (all)	4			
Bacterial tracheitis				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Bronchiolitis				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Device related infection				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Exanthema subitum				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Gastroenteritis				
alternative assessment type: Non-systematic				

subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Gastroenteritis rotavirus			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Pneumonia staphylococcal			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Skin candida			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Tracheitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Viral infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Pneumonia respiratory syncytial viral			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Food intolerance			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Hyperphosphataemia			

subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Hypercalcaemia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Metabolic acidosis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 September 2008	Modification of the inclusion criteria and in the conduct of the trial
20 November 2008	Modification in the PK assessment schedule and in the dosing regimen
12 June 2009	Modification in the dosing schedule and in the conduct of the trial

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/18086009

http://www.ncbi.nlm.nih.gov/pubmed/18318644

http://www.ncbi.nlm.nih.gov/pubmed/22397652