

**Clinical trial results:****A Randomized, Open-Label, Multicenter, Multinational, Dose-Ranging, Historical Control Study of the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of ENB-0040 (Human Recombinant Tissue Nonspecific Alkaline Phosphatase Fusion Protein) in Children With Hypophosphatasia (HPP)****Summary**

EudraCT number	2015-001128-52
Trial protocol	Outside EU/EEA
Global end of trial date	29 July 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-006-09
-----------------------	------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00952484
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@alxn.com
Scientific contact	European Clinical Trial Information, Alexion Europe SAS, +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)	EMA-000987-PIP01-10
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 March 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 July 2010
Global end of trial reached?	Yes
Global end of trial date	29 July 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This clinical trial studied the safety and efficacy of asfotase alfa in children with HPP compared to a historical control group.

Protection of trial subjects:

No specific measure

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 September 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	United States: 25
Worldwide total number of subjects	29
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)	27
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:

Patients were recruited to participate in the study from September to December 2009 at investigational sites via posting in clinicaltrials.gov and contact with physicians experienced in the diagnosis and management of HPP. De-identified historical controls were also selected from a natural history database of patients with HPP.

Pre-assignment

Screening details:

Patients meeting eligibility criteria were randomly assigned to receive 2mg/kg or 3mg/kg of asfotase alfa SC 3 times weekly for 24 weeks.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	2 mg/kg or 3 mg/kg Asfotase Alfa

Arm description:

2 mg/kg or 3 mg/kg subcutaneous (SC) injection three times per week.

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

Dosage and administration details:

2 mg/kg or 3 mg/kg subcutaneous (SC) injection three times per week

Arm title	Historical control
------------------	--------------------

Arm description: -

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	2 mg/kg or 3 mg/kg Asfotase Alfa	Historical control
Started	13	16
Completed	12	16
Not completed	1	0
Consent withdrawn by subject	1	-

Baseline characteristics

Reporting groups

Reporting group title	2 mg/kg or 3 mg/kg Asfotase Alfa
Reporting group description:	2 mg/kg or 3 mg/kg subcutaneous (SC) injection three times per week.
Reporting group title	Historical control
Reporting group description: -	

Reporting group values	2 mg/kg or 3 mg/kg Asfotase Alfa	Historical control	Total
Number of subjects	13	16	29
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)	11	16	27
Adolescents (12-17 years)	2	0	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			
arithmetic mean	8.8	6	
standard deviation	± 2.21	± 1.78	-
Gender categorical			
Units: Subjects			
Female	2	5	7
Male	11	11	22

Subject analysis sets

Subject analysis set title	2 mg/kg SC inj. three times per week
Subject analysis set type	Intention-to-treat
Subject analysis set description:	ITT population, which included all randomized patients that received any treatment with asfotase alfa (2 mg/kg thrice weekly), even if they discontinued or were lost to follow-up during the conduct of the clinical trial.
Subject analysis set title	3 mg/kg SC inj. three times per week
Subject analysis set type	Intention-to-treat
Subject analysis set description:	ITT population, which included all randomized patients that received any treatment with asfotase alfa (3 mg/kg thrice weekly), even if they discontinued or were lost to follow-up during the conduct of the clinical trial.

Reporting group values	2 mg/kg SC inj. three times per week	3 mg/kg SC inj. three times per week	
Number of subjects	6	7	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	5	6	
Adolescents (12-17 years)	1	1	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	8.4	9.1	
standard deviation	± 2.2	± 2.3	
Gender categorical			
Units: Subjects			
Female	1	1	
Male	5	6	

End points

End points reporting groups

Reporting group title	2 mg/kg or 3 mg/kg Asfotase Alfa
Reporting group description:	2 mg/kg or 3 mg/kg subcutaneous (SC) injection three times per week.
Reporting group title	Historical control
Reporting group description: -	
Subject analysis set title	2 mg/kg SC inj. three times per week
Subject analysis set type	Intention-to-treat
Subject analysis set description:	ITT population, which included all randomized patients that received any treatment with asfotase alfa (2 mg/kg thrice weekly), even if they discontinued or were lost to follow-up during the conduct of the clinical trial.
Subject analysis set title	3 mg/kg SC inj. three times per week
Subject analysis set type	Intention-to-treat
Subject analysis set description:	ITT population, which included all randomized patients that received any treatment with asfotase alfa (3 mg/kg thrice weekly), even if they discontinued or were lost to follow-up during the conduct of the clinical trial.

Primary: Change in Rickets Severity on Skeletal Radiographs From Baseline to Week 24 as Measured by the Radiographic Global Impression of Change (RGI-C) Scale

End point title	Change in Rickets Severity on Skeletal Radiographs From Baseline to Week 24 as Measured by the Radiographic Global Impression of Change (RGI-C) Scale
End point description:	A 7-point RGI-C (radiographic global impression of change) score was used to rate change in rickets severity. 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.
End point type	Primary
End point timeframe:	Baseline and Week 24

End point values	2 mg/kg or 3 mg/kg Asfotase Alfa	Historical control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	16		
Units: unit(s)				
median (full range (min-max))	2 (0 to 2.3)	0 (-1.3 to 2)		

Statistical analyses

Statistical analysis title	Statistical analysis 1 for Outcome measure 1
Statistical analysis description:	ITT population, which included randomized patients that received treatment with asfotase alfa, even if discontinued or lost to follow-up. The last assessment prior to Week 24 is used for missing Week 24

data; patients with no post-baseline assessments imputed as having no change. A historical control group is used for comparison.

Comparison groups	2 mg/kg or 3 mg/kg Asfotase Alfa v Historical control
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0007 ^[1]
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - P-value based on Wilcoxon rank sum test comparing the median RGI-C score for the asfotase alfa combined reporting group to the historical control group.

Secondary: Change in Osteomalacia - Osteoid Thickness (as Measured by Trans-iliac Crest Bone Biopsy)

End point title	Change in Osteomalacia - Osteoid Thickness (as Measured by Trans-iliac Crest Bone Biopsy) ^[2]
-----------------	--

End point description:

Change from Baseline to Week 24 in osteoid thickness

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline and Week 24

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The analysis cannot be done for the historical control arm (non-interventional arm).

End point values	2 mg/kg or 3 mg/kg Asfotase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: um				
arithmetic mean (standard deviation)	-3.858 (± 4.2784)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Osteomalacia - Osteoid Volume/Bone Volume (as Measured by Trans-iliac Crest Bone Biopsy)

End point title	Change in Osteomalacia - Osteoid Volume/Bone Volume (as Measured by Trans-iliac Crest Bone Biopsy) ^[3]
-----------------	---

End point description:

Change from Baseline to Week 24 in osteoid volume/bone volume (%), calculated as the absolute difference of the Baseline and Week 24 percentages.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline and Week 24

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The analysis cannot be done for the historical control arm (non-interventional arm).

End point values	2 mg/kg or 3 mg/kg Asfotase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	12 ^[4]			
Units: percent				
arithmetic mean (standard deviation)	-4.225 (\pm 7.5582)			

Notes:

[4] - Asfotase alfa combined

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Osteomalacia - Mineralization Lag Time (as Measured by Trans-iliac Crest Bone Biopsy)

End point title	Change in Osteomalacia - Mineralization Lag Time (as Measured by Trans-iliac Crest Bone Biopsy) ^[5]
-----------------	--

End point description:

Change from Baseline to Week 24 in mineralization lag time.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline and Week 24

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The analysis cannot be done for the historical control arm (non-interventional arm).

End point values	2 mg/kg or 3 mg/kg Asfotase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: days				
arithmetic mean (standard deviation)	20.392 (\pm 208.9814)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Height (Z-scores)

End point title	Change in Height (Z-scores) ^[6]
-----------------	--

End point description:

Change from Baseline to Week 24 in Height Z-Score. Height Z-Scores assigned based on Centers for Disease Control (CDC) growth charts and methodology

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline and Week 24

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The analysis cannot be done for the historical control arm (non-interventional arm).

End point values	2 mg/kg or 3 mg/kg Asfotase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Height Z score				
arithmetic mean (standard deviation)	0.01 (\pm 0.141)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Biomarkers of Asfotase Alfa Activity as Measured by Plasma Inorganic Pyrophosphate (PPi)

End point title	Change in Biomarkers of Asfotase Alfa Activity as Measured by Plasma Inorganic Pyrophosphate (PPi) ^[7]
-----------------	---

End point description:

Change from Baseline to Week 24 in Plasma PPi

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline and Week 24

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The analysis cannot be done for the historical control arm (non-interventional arm).

End point values	2 mg/kg or 3 mg/kg Asfotase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: uM				
arithmetic mean (standard deviation)	-1.883 (\pm 0.7285)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Biomarkers of Asfotase Alfa Activity as Measured by Pyridoxal-5'-Phosphate (PLP)

End point title	Change in Biomarkers of Asfotase Alfa Activity as Measured by
-----------------	---

End point description:

Change from Baseline to Week 24 in Plasma PLP

End point type Secondary

End point timeframe:

Baseline and Week 24

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The analysis cannot be done for the historical control arm (non-interventional arm).

End point values	2 mg/kg or 3 mg/kg Asfotase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: ng/mL				
arithmetic mean (standard deviation)	-164.533 (\pm 121.484)			

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).^[9]

End point description:

Maximum serum concentration observed following single dose of asfotase alfa.

End point type Secondary

End point timeframe:

Study Week 1 (0 to 48 hours post-dose)

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The analysis cannot be done for the historical control arm (non-interventional arm).

End point values	2 mg/kg or 3 mg/kg Asfotase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	13 ^[10]			
Units: U/L				
arithmetic mean (standard deviation)				
2 mg/kg SC inj. three times per week	566 (\pm 120)			
3 mg/kg SC inj. three times per week	1260 (\pm 439)			

Notes:

[10] - 2 mg/kg SC inj. 3 times/week: 6 patients analysed
3 mg/kg SC inj. 3 times/week: 7 patients 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) ^[11]
-----------------	---

End point description:

Maximum serum concentration observed following single dose of asfotase alfa.

End point type	Secondary
----------------	-----------

End point timeframe:

Study Week 1 (0 to 48 hours post-dose)

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis cannot be done for the historical control arm (non-interventional arm).

End point values	2 mg/kg or 3 mg/kg Asfotase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	13 ^[12]			
Units: hours				
arithmetic mean (standard deviation)				
2 mg/kg SC inj. three times per week	37.2 (± 8.1)			
3 mg/kg SC inj. three times per week	34.3 (± 6)			

Notes:

[12] - 2 mg/kg SC inj. 3 times/week: 6 patients analysed

3 mg/kg SC inj. 3 times/week: 7 patients 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) ^[13]
-----------------	--

End point description:

Area under serum concentration-time curve to last measurable concentration following single dose of asfotase alfa.

End point type	Secondary
----------------	-----------

End point timeframe:

Study Week 1 (0 to 48 hours post-dose)

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis cannot be done for the historical control arm (non-interventional arm).

End point values	2 mg/kg or 3 mg/kg Asfotase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	13 ^[14]			
Units: h*U/L				
arithmetic mean (standard deviation)				
2 mg/kg SC inj. three times per week	19700 (± 5720)			
3 mg/kg SC inj. three times per week	45200 (± 15100)			

Notes:

[14] - 2 mg/kg SC inj. 3 times/week: 6 patients analysed
3 mg/kg SC inj. 3 times/week: 7 patients analysed

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). ^[15]
End point description:	Maximum serum concentration observed following multiple doses of asfotase alfa.
End point type	Secondary
End point timeframe:	Study Week 6 (0 to 48 hours post-dose)

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis cannot be done for the historical control arm (non-interventional arm).

End point values	2 mg/kg or 3 mg/kg Asfotase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	13 ^[16]			
Units: U/L				
arithmetic mean (standard deviation)				
2 mg/kg SC inj. three times per week	1780 (± 666)			
3 mg/kg SC inj. three times per week	2280 (± 875)			

Notes:

[16] - 2 mg/kg SC inj. 3 times/week: 6 patients analysed
3 mg/kg SC inj. 3 times/week: 7 patients 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). ^[17]
End point description:	Time at maximum serum concentration observed following multiple doses of asfotase alfa.
End point type	Secondary

End point timeframe:

Study Week 6 (0 to 48 hours post-dose)

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis cannot be done for the historical control arm (non-interventional arm).

End point values	2 mg/kg or 3 mg/kg Asfotase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	13 ^[18]			
Units: hours				
arithmetic mean (standard deviation)				
2 mg/kg SC inj. three times per week	20.8 (± 10)			
3 mg/kg SC inj. three times per week	17.3 (± 8.6)			

Notes:

[18] - 2 mg/kg SC inj. 3 times/week: 6 patients analysed

3 mg/kg SC inj. 3 times/week: 7 patients 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) ^[19]
-----------------	--

End point description:

Area under serum concentration-time curve to last measurable concentration following multiple doses of asfotase alfa.

End point type	Secondary
----------------	-----------

End point timeframe:

Study Week 6 (0 to 48 hours post-dose).

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis cannot be done for the historical control arm (non-interventional arm).

End point values	2 mg/kg or 3 mg/kg Asfotase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	13 ^[20]			
Units: h*U/L				
arithmetic mean (standard deviation)				
2 mg/kg SC inj. three times per week	76000 (± 28100)			
3 mg/kg SC inj. three times per week	94200 (± 44400)			

Notes:

[20] - 2 mg/kg SC inj. 3 times/week: 6 patients analysed

3 mg/kg SC inj. 3 times/week: 7 patients analysed

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

res6 months

Adverse event reporting additional description:

Adverse event data for the historical control group were not collected.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	13
--------------------	----

Reporting groups

Reporting group title	2 mg/kg Asfotase Alfa
-----------------------	-----------------------

Reporting group description:

2 mg/kg subcutaneous (SC) injection three times per week.

Reporting group title	3 mg/kg Asfotase Alfa
-----------------------	-----------------------

Reporting group description:

3 mg/kg subcutaneous (SC) injection three times per week.

Serious adverse events	2 mg/kg Asfotase Alfa	3 mg/kg Asfotase Alfa	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	2 mg/kg Asfotase Alfa	3 mg/kg Asfotase Alfa	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	7 / 7 (100.00%)	
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	5 / 6 (83.33%)	7 / 7 (100.00%)	
occurrences (all)	13	16	
Injection site discolouration			
subjects affected / exposed	4 / 6 (66.67%)	4 / 7 (57.14%)	
occurrences (all)	4	4	
Injection site pruritus			

alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 6 (66.67%)	3 / 7 (42.86%)	
occurrences (all)	8	3	
Injection site swelling			
subjects affected / exposed	1 / 6 (16.67%)	2 / 7 (28.57%)	
occurrences (all)	3	2	
Infusion site pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Injection site pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 6 (50.00%)	3 / 7 (42.86%)	
occurrences (all)	5	5	
Oedema peripheral			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
infection site hemorrhage			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Infection site nodule			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Irritability			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			

Seasonal allergy alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 7 (14.29%) 1	
Hypersensitivity subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 7 (0.00%) 0	
Nasopharyngitis alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 3	0 / 7 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders			
Cough alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	2 / 7 (28.57%) 2	
Oropharyngeal pain alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 3	1 / 7 (14.29%) 1	
Nasal congestion alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 7 (14.29%) 1	
Rhinorrhoea alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	2 / 7 (28.57%) 2	
Epistaxis alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 7 (14.29%) 6	
Rhinitis allergic alternative assessment type: Non-systematic			

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 7 (14.29%) 1	
Psychiatric disorders Anxiety alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 7 (0.00%) 0	
Investigations Blood 1,25-dihydroxycholecalciferol decreased subjects affected / exposed occurrences (all) Blood 25-hydroxycholecalciferol decreased subjects affected / exposed occurrences (all) Vitamin B6 decreased subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0 1 / 6 (16.67%) 1 0 / 6 (0.00%) 0	1 / 7 (14.29%) 1 0 / 7 (0.00%) 0 1 / 7 (14.29%) 1	
Injury, poisoning and procedural complications Procedural pain subjects affected / exposed occurrences (all) Excoriation alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Animal bite alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Tongue injury alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Fall alternative assessment type: Non-	4 / 6 (66.67%) 4 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0	3 / 7 (42.86%) 3 2 / 7 (28.57%) 2 1 / 7 (14.29%) 1 1 / 7 (14.29%) 1	

systematic			
subjects affected / exposed	3 / 6 (50.00%)	0 / 7 (0.00%)	
occurrences (all)	3	0	
Foreign body			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Laceration			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Limb injury			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 6 (33.33%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Procedural nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 6 (33.33%)	1 / 7 (14.29%)	
occurrences (all)	5	1	
Eye disorders			
Scleral haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Eye allergy			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Vomiting			
alternative assessment type: Non-systematic			

subjects affected / exposed	4 / 6 (66.67%)	1 / 7 (14.29%)
occurrences (all)	8	1
Dental caries		
alternative assessment type: Non-systematic		
subjects affected / exposed	1 / 6 (16.67%)	1 / 7 (14.29%)
occurrences (all)	1	1
Gastrooesophageal reflux disease		
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	1
Sensitivity of teeth		
alternative assessment type: Non-systematic		
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	1
Teething		
alternative assessment type: Non-systematic		
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	1
Toothache		
alternative assessment type: Non-systematic		
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	2
Anal fissure		
alternative assessment type: Non-systematic		
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	1	0
Diarrhoea		
alternative assessment type: Non-systematic		
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	1	0
Nausea		
alternative assessment type: Non-systematic		
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	1	0
Tooth loss		
alternative assessment type: Non-		

systematic			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Dermatitis contact			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 6 (16.67%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Sinus congestion			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 6 (33.33%)	1 / 7 (14.29%)	
occurrences (all)	2	1	
Medial tibial stress syndrome			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Unequal limb length			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Arthralgia			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 6 (33.33%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Back pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Myalgia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	

<p>Neck pain</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 6 (16.67%)</p> <p>1</p>	<p>0 / 7 (0.00%)</p> <p>0</p>	
<p>Infections and infestations</p> <p>Upper respiratory tract infection</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Otitis media</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Sinusitis</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Otitis externa</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Gastroenteritis viral</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 6 (16.67%)</p> <p>1</p> <p>1 / 6 (16.67%)</p> <p>1</p> <p>1 / 6 (16.67%)</p> <p>2</p> <p>0 / 6 (0.00%)</p> <p>0</p> <p>1 / 6 (16.67%)</p> <p>1</p>	<p>3 / 7 (42.86%)</p> <p>3</p> <p>1 / 7 (14.29%)</p> <p>1</p> <p>1 / 7 (14.29%)</p> <p>1</p> <p>1 / 7 (14.29%)</p> <p>1</p> <p>0 / 7 (0.00%)</p> <p>0</p>	
<p>Metabolism and nutrition disorders</p> <p>Decreased appetite</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 6 (16.67%)</p> <p>1</p>	<p>0 / 7 (0.00%)</p> <p>0</p>	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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>