



Clinical trial results:

A Randomized, Open-Label, Multicenter, Multinational, Dose-Ranging, Concurrent Control Study of the Safety, Efficacy, and Pharmacokinetics of ENB-0040 (Human Recombinant Tissue-Nonspecific Alkaline Phosphatase Fusion Protein) in Adolescents and Adults with Hypophosphatasia (HPP)

Summary

EudraCT number	2017-001831-38
Trial protocol	Outside EU/EEA
Global end of trial date	28 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-009-10
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01163149
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)	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	28 June 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 June 2016
Global end of trial reached?	Yes
Global end of trial date	28 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This clinical trial was conducted to study hypophosphatasia (HPP), a bone disorder caused by gene mutations or changes. These gene mutations cause low levels of an enzyme needed to harden bone. The purpose of this study was to test the safety and efficacy of 2 doses of the study drug called asfotase alfa as compared to a control group to see effects on adolescents and adults with HPP.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 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: 8
Country: Number of subjects enrolled	United States: 11
Worldwide total number of subjects	19
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)	0
Adolescents (12-17 years)	6
Adults (18-64 years)	13
From 65 to 84 years	0

85 years and over	0
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Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

19 patients, who had HPP, a bone disorder caused by gene mutations or changes, were enrolled in this study.

Period 1

Period 1 title	Primary Treatment (First 24 Weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	0.3 mg/kg Asfotase Alfa (Primary Treatment)

Arm description:

Asfotase alfa Cohort 1: Daily subcutaneous (SC) injections of 0.3 milligrams (mg)/kilograms (kg) asfotase alfa (2.1 mg/kg/week total) during Primary Treatment Period through Week 24. Following completion of the Week 24 visit, all patients were eligible to participate in an open-label extension treatment period. In this extension period, all patients were treated with daily SC injections of 0.5 mg/kg/day asfotase alfa (a total of 3.5 mg/kg/week) for approximately 24 weeks, then patients received 1 mg/kg/day 6 days/week until regulatory approval of the drug.

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:

Cohort 1: 0.3 mg/kg (2.1 mg/kg/week total)

Arm title	0.5 mg/kg Asfotase Alfa (Primary Treatment)
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Arm description:

Asfotase alfa Cohort 2: Daily SC injections of 0.5 mg/kg asfotase alfa (3.5 mg/kg/week total) during Primary Treatment Period through Week 24. Following completion of the Week 24 visit, all patients were eligible to participate in an open-label extension treatment period. In this extension period, all patients were treated with daily SC injections of 0.5 mg/kg/day asfotase alfa (a total of 3.5 mg/kg/week) for approximately 24 weeks, then patients received 1 mg/kg/day 6 days/week until regulatory approval of the drug.

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:

Cohort 2: 0.5 mg/kg (3.5 mg/kg/week total)

Arm title	Concurrent Control (Primary Treatment)
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Arm description:

No asfotase alfa during first 24 weeks (primary treatment period). Following completion of the Week 24 visit, all patients randomized to the concurrent control cohort were eligible to participate in an open-label extension treatment period. In this extension period, all patients were treated with daily SC

injections of 0.5 mg/kg/day asfotase alfa (a total of 3.5 mg/kg/week) for approximately 24 weeks, then patients received 1 mg/kg/day 6 days/week until regulatory approval of the drug.

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

Number of subjects in period 1	0.3 mg/kg Asfotase Alfa (Primary Treatment)	0.5 mg/kg Asfotase Alfa (Primary Treatment)	Concurrent Control (Primary Treatment)
Started	7	6	6
Received at Least 1 Dose of Study Drug	7	6	6
Completed	7	6	6

Period 2

Period 2 title	Extension Treatment
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Asfotase Alfa Combined (Extension Treatment)
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Arm description:

In this extension period, all patients were treated with daily SC injections of 0.5 mg/kg/day asfotase alfa (a total of 3.5 mg/kg/week) for approximately 24 weeks, then patients received 1 mg/kg/day 6 days/week until regulatory approval of the drug. Patients treated during the Extension Period were from Cohort 1 (Number [N]=7), Cohort 2 (N=6), and the Control group (N=6) combined; total N=19.

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:

In the open label extension period, all patients were treated with 0.5 mg/kg/day asfotase alfa (a total of 3.5 mg/kg/week) for approximately 24 weeks, then patients received 1 mg/kg/day 6 days/week until regulatory approval of the drug.

Number of subjects in period 2	Asfotase Alfa Combined (Extension Treatment)
Started	19
Received at Least 1 Dose of Study Drug	19
Completed	14
Not completed	5
Adverse event, non-fatal	1
Consent withdrawn by patient	3
Noncompliance	1

Baseline characteristics

Reporting groups

Reporting group title	0.3 mg/kg Asfotase Alfa (Primary Treatment)
Reporting group description:	
Asfotase alfa Cohort 1: Daily subcutaneous (SC) injections of 0.3 milligrams (mg)/kilograms (kg) asfotase alfa (2.1 mg/kg/week total) during Primary Treatment Period through Week 24. Following completion of the Week 24 visit, all patients were eligible to participate in an open-label extension treatment period. In this extension period, all patients were treated with daily SC injections of 0.5 mg/kg/day asfotase alfa (a total of 3.5 mg/kg/week) for approximately 24 weeks, then patients received 1 mg/kg/day 6 days/week until regulatory approval of the drug.	
Reporting group title	0.5 mg/kg Asfotase Alfa (Primary Treatment)
Reporting group description:	
Asfotase alfa Cohort 2: Daily SC injections of 0.5 mg/kg asfotase alfa (3.5 mg/kg/week total) during Primary Treatment Period through Week 24. Following completion of the Week 24 visit, all patients were eligible to participate in an open-label extension treatment period. In this extension period, all patients were treated with daily SC injections of 0.5 mg/kg/day asfotase alfa (a total of 3.5 mg/kg/week) for approximately 24 weeks, then patients received 1 mg/kg/day 6 days/week until regulatory approval of the drug.	
Reporting group title	Concurrent Control (Primary Treatment)
Reporting group description:	
No asfotase alfa during first 24 weeks (primary treatment period). Following completion of the Week 24 visit, all patients randomized to the concurrent control cohort were eligible to participate in an open-label extension treatment period. In this extension period, all patients were treated with daily SC injections of 0.5 mg/kg/day asfotase alfa (a total of 3.5 mg/kg/week) for approximately 24 weeks, then patients received 1 mg/kg/day 6 days/week until regulatory approval of the drug.	

Reporting group values	0.3 mg/kg Asfotase Alfa (Primary Treatment)	0.5 mg/kg Asfotase Alfa (Primary Treatment)	Concurrent Control (Primary Treatment)
Number of subjects	7	6	6
Age categorical			
Units: Subjects			
Adolescent (12-17 years)	2	1	3
Adult (18 years or older)	5	5	3
Age continuous			
Units: years			
median	45	55	21
full range (min-max)	14 to 66	15 to 57	13 to 58
Gender categorical			
Units: Subjects			
Female	6	4	2
Male	1	2	4
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	7	6	5
More than one race	0	0	0
Unknown or Not Reported	0	0	1
Ethnicity (NIH/OMB)			

Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	7	6	6
Unknown or Not Reported	0	0	0
Hypophosphatasia (HPP) Phenotype			
Units: Subjects			
Infantile (<6 months)	1	2	1
Juvenile (≥6 months to <18 years)	5	4	5
Adult (≥ 18 years)	1	0	0
Age at Onset of Symptoms			
Units: years			
median	2	2	0.88
full range (min-max)	0.2 to 36	0 to 3	0.2 to 4

Reporting group values	Total		
Number of subjects	19		
Age categorical			
Units: Subjects			
Adolescent (12-17 years)	6		
Adult (18 years or older)	13		
Age continuous			
Units: years			
median			
full range (min-max)	-		
Gender categorical			
Units: Subjects			
Female	12		
Male	7		
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	0		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	0		
White	18		
More than one race	0		
Unknown or Not Reported	1		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	0		
Not Hispanic or Latino	19		
Unknown or Not Reported	0		
Hypophosphatasia (HPP) Phenotype			
Units: Subjects			
Infantile (<6 months)	4		
Juvenile (≥6 months to <18 years)	14		
Adult (≥ 18 years)	1		
Age at Onset of Symptoms			
Units: years			
median			

full range (min-max)	-		
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End points

End points reporting groups

Reporting group title	0.3 mg/kg Asfotase Alfa (Primary Treatment)
Reporting group description: Asfotase alfa Cohort 1: Daily subcutaneous (SC) injections of 0.3 milligrams (mg)/kilograms (kg) asfotase alfa (2.1 mg/kg/week total) during Primary Treatment Period through Week 24. Following completion of the Week 24 visit, all patients were eligible to participate in an open-label extension treatment period. In this extension period, all patients were treated with daily SC injections of 0.5 mg/kg/day asfotase alfa (a total of 3.5 mg/kg/week) for approximately 24 weeks, then patients received 1 mg/kg/day 6 days/week until regulatory approval of the drug.	
Reporting group title	0.5 mg/kg Asfotase Alfa (Primary Treatment)
Reporting group description: Asfotase alfa Cohort 2: Daily SC injections of 0.5 mg/kg asfotase alfa (3.5 mg/kg/week total) during Primary Treatment Period through Week 24. Following completion of the Week 24 visit, all patients were eligible to participate in an open-label extension treatment period. In this extension period, all patients were treated with daily SC injections of 0.5 mg/kg/day asfotase alfa (a total of 3.5 mg/kg/week) for approximately 24 weeks, then patients received 1 mg/kg/day 6 days/week until regulatory approval of the drug.	
Reporting group title	Concurrent Control (Primary Treatment)
Reporting group description: No asfotase alfa during first 24 weeks (primary treatment period). Following completion of the Week 24 visit, all patients randomized to the concurrent control cohort were eligible to participate in an open-label extension treatment period. In this extension period, all patients were treated with daily SC injections of 0.5 mg/kg/day asfotase alfa (a total of 3.5 mg/kg/week) for approximately 24 weeks, then patients received 1 mg/kg/day 6 days/week until regulatory approval of the drug.	
Reporting group title	Asfotase Alfa Combined (Extension Treatment)
Reporting group description: In this extension period, all patients were treated with daily SC injections of 0.5 mg/kg/day asfotase alfa (a total of 3.5 mg/kg/week) for approximately 24 weeks, then patients received 1 mg/kg/day 6 days/week until regulatory approval of the drug. Patients treated during the Extension Period were from Cohort 1 (Number [N]=7), Cohort 2 (N=6), and the Control group (N=6) combined; total N=19.	
Subject analysis set title	Asfotase Alfa Combined (Primary Treatment)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients treated during the Primary Treatment Period were from Cohort 1 (N=7) and Cohort 2 (N=6) combined; total N=13.	

Primary: Change From Baseline To Week 24 For Plasma Pyridoxal-5' Phosphate (PLP)

End point title	Change From Baseline To Week 24 For Plasma Pyridoxal-5' Phosphate (PLP)
End point description: Blood samples were collected to evaluate the effect of asfotase alfa on reduction in plasma pyridoxal-5' phosphate (PLP).	
End point type	Primary
End point timeframe: Baseline, Week 24	

End point values	0.3 mg/kg Asfotase Alfa (Primary Treatment)	0.5 mg/kg Asfotase Alfa (Primary Treatment)	Concurrent Control (Primary Treatment)	Asfotase Alfa Combined (Primary Treatment)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	7	6	6	13
Units: ng/mL				
arithmetic mean (standard deviation)	-254.96 (± 196.206)	-564.27 (± 624.009)	3.13 (± 242.721)	-397.72 (± 455.249)

Statistical analyses

Statistical analysis title	Change From Baseline To Week 24 For PLP
Statistical analysis description: Change from Baseline to Week 24 for Plasma Pyridoxal-5' Phosphate (PLP)	
Comparison groups	Concurrent Control (Primary Treatment) v Asfotase Alfa Combined (Primary Treatment)
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.0285 ^[2]
Method	Wilcoxon rank-sum
Confidence interval	
level	95 %
sides	2-sided
lower limit	-626.4
upper limit	-59.2

Notes:

[1] - If p-values were less than 0.05 and the Hodges-Lehman-Sen estimate (-302.05) favored asfotase alfa (that is, it had a negative sign indicating the between-group differences in change from Baseline favored treated patients), then superiority over control was claimed.

[2] - Two-sided with p-value threshold <0.05 for statistical significance

Primary: Change From Baseline To Week 24 For Plasma Inorganic Pyrophosphate (PPi)

End point title	Change From Baseline To Week 24 For Plasma Inorganic Pyrophosphate (PPi)
End point description: Blood samples were collected to evaluate the effect of asfotase alfa on reduction in plasma inorganic pyrophosphate (PPi).	
End point type	Primary
End point timeframe: Baseline, Week 24	

End point values	0.3 mg/kg Asfotase Alfa (Primary Treatment)	0.5 mg/kg Asfotase Alfa (Primary Treatment)	Concurrent Control (Primary Treatment)	Asfotase Alfa Combined (Primary Treatment)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	7	6	6	13
Units: uM				
arithmetic mean (standard deviation)	-2.027 (\pm 1.4381)	-2.185 (\pm 1.3304)	-1.052 (\pm 2.9248)	-2.100 (\pm 1.3335)

Statistical analyses

Statistical analysis title	Change From Baseline To Week 24 For PPi
Statistical analysis description: Change From Baseline to Week 24 for Plasma Inorganic Pyrophosphate (PPi)	
Comparison groups	Concurrent Control (Primary Treatment) v Asfotase Alfa Combined (Primary Treatment)
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	= 0.0715 ^[4]
Method	Wilcoxon rank-sum
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.21
upper limit	0.23

Notes:

[3] - If p-values were less than 0.05 and the Hodges-Lehman-Sen estimate (-1.825) favored asfotase alfa (that is, it had a negative sign indicating the between-group differences in change from Baseline favored treated patients), then superiority over control was claimed.

[4] - Two-sided with p-value threshold <0.05 for statistical significance

Primary: Safety And Tolerability Of Asfotase Alfa

End point title	Safety And Tolerability Of Asfotase Alfa ^[5]
End point description: The safety and tolerability of daily subcutaneous (SC) injections of asfotase alfa was assessed by routine monitoring of patients for treatment-emergent adverse events (TEAEs) and injection associated reactions (IARs).	
End point type	Primary
End point timeframe: Up to 288 weeks exposure to asfotase alfa	

Notes:

[5] - 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: Statistical analyses data were not calculated for adverse events per study protocol.

End point values	0.3 mg/kg Asfotase Alfa (Primary Treatment)	0.5 mg/kg Asfotase Alfa (Primary Treatment)	Concurrent Control (Primary Treatment)	Asfotase Alfa Combined (Extension Treatment)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	6	6	19
Units: Number of Treatment-Emergent Events				
Any TEAE	243	81	45	1145
Not related TEAE	110	69	45	731
Related TEAE	133	12	0	414
Injection Site Reactions	133	12	0	385
Serious TEAEs	1	1	4	29
TEAEs leading to withdrawal	0	0	0	2
Deaths	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Bone Mineral Content (BMC) As Measured By Dual-energy X-ray Absorptiometry (DXA) To Week 24

End point title	Change From Baseline In Bone Mineral Content (BMC) As Measured By Dual-energy X-ray Absorptiometry (DXA) To Week 24
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End point description:

A DXA scan was performed to evaluate BMC of the spine, hip, and whole body during the primary (first 24 weeks) treatment period. The number (N) of patients evaluated for the various time points differ from the total number of patients in the group. The N of patients evaluated is reported in the Category Title.

End point type	Secondary
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End point timeframe:

Baseline, Week 24

End point values	0.3 mg/kg Asfotase Alfa (Primary Treatment)	0.5 mg/kg Asfotase Alfa (Primary Treatment)	Concurrent Control (Primary Treatment)	Asfotase Alfa Combined (Primary Treatment)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	7	6	6	13
Units: grams (g)				
arithmetic mean (standard deviation)				
Hip Total BMC Week 24, N=4, 5, 4, 9	-3.288 (± 7.7669)	1.214 (± 2.2154)	1.288 (± 0.9161)	-0.787 (± 5.5411)
Lumbar Spine BMC Week 24, N=7, 5, 5, 12	2.477 (± 2.5616)	2.768 (± 2.0007)	1.432 (± 1.7824)	2.598 (± 2.2488)
Whole Body BMC Week 24, N=7, 5, 5, 12	-21.871 (± 35.4370)	41.454 (± 20.0358)	237.248 (± 414.0877)	4.514 (± 43.5228)

Statistical analyses

Statistical analysis title	Hip Total BMC Change From Baseline To Week 24
Statistical analysis description: Change From Baseline to Week 24 in Hip Total BMC as Measured by DXA	
Comparison groups	Concurrent Control (Primary Treatment) v Asfotase Alfa Combined (Primary Treatment)
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority ^[6]
P-value	= 0.3301 ^[7]
Method	Wilcoxon rank-sum
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.32
upper limit	1.78

Notes:

[6] - The Hodges-Lehman-Sen estimate = -0.910.

[7] - Two-sided with p-value threshold <0.05 for statistical significance

Statistical analysis title	Lumbar Spine BMC Change From Baseline To Week 24
Statistical analysis description: Change From Baseline to Week 24 in Lumbar Spine BMC as Measured by DXA	
Comparison groups	Concurrent Control (Primary Treatment) v Asfotase Alfa Combined (Primary Treatment)
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority ^[8]
P-value	= 0.3827 ^[9]
Method	Wilcoxon rank-sum
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.36
upper limit	3.12

Notes:

[8] - The Hodges-Lehman-Sen estimate = 1.330.

[9] - Two-sided with p-value threshold <0.05 for statistical significance

Statistical analysis title	Whole Body BMC Change From Baseline To Week 24
Statistical analysis description: Change From Baseline to Week 24 in Whole Body BMC as Measured by DXA	
Comparison groups	Concurrent Control (Primary Treatment) v Asfotase Alfa Combined (Primary Treatment)

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority ^[10]
P-value	= 0.0485 ^[11]
Method	Wilcoxon rank-sum
Confidence interval	
level	95 %
sides	2-sided
lower limit	-917.44
upper limit	-1.74

Notes:

[10] - The Hodges-Lehman-Sen estimate = -77.100.

[11] - Two-sided with p-value threshold <0.05 for statistical significance

Secondary: Change From Baseline In BMC As Measured By DXA From Week 48 Until Week 288

End point title	Change From Baseline In BMC As Measured By DXA From Week 48 Until Week 288
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End point description:

A DXA scan was performed to evaluate BMC of the spine, hip, and whole body during the extension treatment period (up to 288 weeks, including a last overall exposure [LOE]). The N of patients evaluated for the various time points differ from the total number of patients in the group. The N of patients evaluated is reported in the Category Title.

End point type	Secondary
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End point timeframe:

Baseline, every 24 weeks from Week 48 through Week 96, and from Week 144 every 48 weeks until Week 288

End point values	0.3 mg/kg Asfotase Alfa (Primary Treatment)	0.5 mg/kg Asfotase Alfa (Primary Treatment)	Concurrent Control (Primary Treatment)	Asfotase Alfa Combined (Extension Treatment)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7 ^[12]	6 ^[13]	6 ^[14]	19 ^[15]
Units: grams				
arithmetic mean (standard deviation)				
Hip Total BMC Week 48, N=1, 1, 4, 6	1.160 (± 0.0)	4.530 (± 0.0)	2.320 (± 1.3990)	2.495 (± 1.5438)
Hip Total BMC Week 96, N=4, 4, 3, 11	0.082 (± 1.4046)	4.345 (± 4.0466)	2.907 (± 2.0087)	2.403 (± 3.1702)
Hip Total BMC Week 144, N=3, 4, 3, 10	1.630 (± 1.8719)	5.043 (± 5.5955)	4.533 (± 1.4621)	3.866 (± 3.7577)
Hip Total BMC Week 192, N=2, 4, 3, 9	1.080 (± 2.0082)	4.725 (± 6.4843)	2.910 (± 0.2910)	3.310 (± 4.3124)
Hip Total BMC Week 240, N=2, 3, 3, 8	0.550 (± 2.4042)	6.807 (± 5.7557)	-0.673 (± 0.1644)	2.438 (± 4.8626)
Hip Total BMC Week 288, N=0, 1, 0, 1	0.0 (± 0.0)	-2.780 (± 0.0)	0.0 (± 0.0)	-2.780 (± 0.0)
Hip Total BMC LOE, N=4, 5, 4, 13	0.080 (± 1.8713)	3.604 (± 5.8284)	0.328 (± 2.0062)	1.512 (± 4.0224)
Lumbar Spine BMC Week 48, N=1, 1, 5, 7	2.420 (± 0.0)	5.550 (± 0.0)	4.842 (± 5.7882)	4.597 (± 4.8298)
Lumbar Spine BMC Week 96, N=7, 5, 4, 16	3.356 (± 4.4566)	4.174 (± 3.7068)	7.330 (± 5.6953)	4.605 (± 4.5680)

Lumbar Spine BMC Week 144, N=5, 5, 4, 14	2.086 (± 5.2198)	5.828 (± 3.9791)	6.710 (± 4.0174)	4.744 (± 4.6193)
Lumbar Spine BMC Week 192, N=5, 5, 4, 14	2.094 (± 16.4419)	6.162 (± 4.1628)	5.197 (± 5.7568)	4.434 (± 9.9797)
Lumbar Spine BMC Week 240, N=5, 4, 4, 13	3.536 (± 17.0957)	3.298 (± 2.4931)	5.037 (± 4.7161)	3.925 (± 10.2539)
Lumbar Spine BMC Week 288, N=1, 1, 0, 2	20.910 (± 0.0)	6.500 (± 0.0)	0.0 (± 0.0)	13.705 (± 10.1894)
Lumbar Spine BMC LOE, N=7, 5, 5, 17	4.306 (± 14.5714)	5.130 (± 3.5930)	6.714 (± 5.1113)	5.256 (± 9.5103)
Whole Body BMC Week 48, N=1, 1, 5, 7	49.820 (± 0.0)	72.530 (± 0.0)	30.228 (± 82.4369)	39.070 (± 69.2934)
Whole Body BMC Week 96, N=7, 5, 4, 16	7.537 (± 74.2838)	59.604 (± 97.9214)	98.018 (± 111.9259)	46.428 (± 93.5046)
Whole Body BMC Week 144, N=5, 5, 4, 14	-48.236 (± 111.6604)	17.446 (± 173.3574)	92.063 (± 107.9837)	15.307 (± 138.3534)
Whole Body BMC Week 192, N=5, 5, 4, 14	-121.916 (± 92.0001)	23.938 (± 195.8402)	50.375 (± 99.6281)	-20.599 (± 151.5153)
Whole Body BMC Week 240, N=5, 4, 4, 13	-97.706 (± 106.6581)	82.310 (± 223.0794)	40.572 (± 162.1575)	0.231 (± 172.0218)
Whole Body BMC Week 288, N=1, 1, 0, 2	-243.080 (± 0.0)	-144.660 (± 0.0)	0.0 (± 0.0)	-193.870 (± 69.5934)
Whole Body BMC LOE, N=7, 5, 5, 17	-113.296 (± 178.8050)	11.252 (± 217.5674)	82.548 (± 128.7017)	-19.063 (± 188.0498)

Notes:

[12] - "0.0" entered for arithmetic mean for no data and for standard deviation when number (N) = 1.

[13] - "0.0" entered for arithmetic mean for no data and for standard deviation when number (N) = 1.

[14] - "0.0" entered for arithmetic mean for no data and for standard deviation when number (N) = 1.

[15] - "0.0" entered for arithmetic mean for no data and for standard deviation when number (N) = 1.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Bone Mineral Density (BMD) As Measured By Dual-energy X-ray Absorptiometry (DXA) To Week 24

End point title	Change From Baseline In Bone Mineral Density (BMD) As Measured By Dual-energy X-ray Absorptiometry (DXA) To Week 24
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End point description:

A DXA scan was performed to evaluate BMD of the spine, hip, and whole body during the primary (first 24 weeks) treatment period. The N of patients evaluated for the various time points differ from the total number of patients in the group. The N of patients evaluated is reported in the Category Title.

End point type	Secondary
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End point timeframe:

Baseline, Week 24

End point values	0.3 mg/kg Asfotase Alfa (Primary Treatment)	0.5 mg/kg Asfotase Alfa (Primary Treatment)	Concurrent Control (Primary Treatment)	Asfotase Alfa Combined (Primary Treatment)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	7	6	6	13
Units: grams/centimeters squared (g/m2)				
arithmetic mean (standard deviation)				

Hip Total BMD Week 24, N=4, 5, 4, 9	0.0447 (\pm 0.07710)	0.0094 (\pm 0.02441)	0.0195 (\pm 0.01642)	0.0251 (\pm 0.05361)
Lumbar Spine BMD Week 24, N=7, 5, 5, 12	0.0269 (\pm 0.02113)	0.0272 (\pm 0.01492)	0.0098 (\pm 0.02475)	0.0270 (\pm 0.01802)
Whole Body BMD Week 24, N=7, 5, 5, 12	-0.0003 (\pm 0.01788)	-0.0122 (\pm 0.01055)	0.0206 (\pm 0.03173)	-0.0052 (\pm 0.01589)

Statistical analyses

Statistical analysis title	Hip Total BMD Change From Baseline To Week 24
Statistical analysis description: Change From Baseline to Week 24 in Hip Total BMD as Measured by DXA	
Comparison groups	Concurrent Control (Primary Treatment) v Asfotase Alfa Combined (Primary Treatment)
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority ^[16]
P-value	= 0.7357 ^[17]
Method	Wilcoxon rank-sum
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.039

Notes:

[16] - The Hodges-Lehman-Sen estimate = -0.0125.

[17] - Two-sided with p-value threshold <0.05 for statistical significance

Statistical analysis title	Lumbar Spine BMD Change From Baseline To Week 24
Statistical analysis description: Change From Baseline to Week 24 in Lumbar Spine BMD as Measured by DXA	
Comparison groups	Concurrent Control (Primary Treatment) v Asfotase Alfa Combined (Primary Treatment)
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority ^[18]
P-value	= 0.2439 ^[19]
Method	Wilcoxon rank-sum
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.009
upper limit	0.041

Notes:

[18] - The Hodges-Lehman-Sen estimate = 0.0255.

[19] - Two-sided with p-value threshold <0.05 for statistical significance

Statistical analysis title	Whole Body BMD Change From Baseline To Week 24
Statistical analysis description: Change From Baseline to Week 24 in Whole Body BMD as Measured by DXA	
Comparison groups	Concurrent Control (Primary Treatment) v Asfotase Alfa

	Combined (Primary Treatment)
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority ^[20]
P-value	= 0.1222 ^[21]
Method	Wilcoxon rank-sum
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.059
upper limit	0.012

Notes:

[20] - The Hodges-Lehman-Sen estimate = -0.0315.

[21] - Two-sided with p-value threshold <0.05 for statistical significance

Secondary: Change From Baseline In BMD As Measured By DXA From Week 48 Until Week 288

End point title	Change From Baseline In BMD As Measured By DXA From Week 48 Until Week 288
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End point description:

A DXA scan was performed to evaluate BMD of the spine, hip, and whole body during the extension treatment period (up to 288 weeks, including an LOE). The N of patients evaluated for the various time points differ from the total number of patients in the group. The N of patients evaluated is reported in the Category Title.

End point type	Secondary
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End point timeframe:

Baseline, every 24 weeks from Week 48 through Week 96, and from Week 144 every 48 weeks until Week 288

End point values	0.3 mg/kg Asfotase Alfa (Primary Treatment)	0.5 mg/kg Asfotase Alfa (Primary Treatment)	Concurrent Control (Primary Treatment)	Asfotase Alfa Combined (Extension Treatment)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7 ^[22]	6 ^[23]	6 ^[24]	19 ^[25]
Units: g/cm ²				
arithmetic mean (standard deviation)				
Hip Total BMD Week 48, N=1, 1, 4, 6	0.0190 (± 0.0)	0.0240 (± 0.0)	0.0590 (± 0.04109)	0.0465 (± 0.03729)
Hip Total BMD Week 96, N=4, 4, 3, 11	0.0003 (± 0.00532)	0.0780 (± 0.06703)	0.0480 (± 0.04943)	0.0415 (± 0.05542)
Hip Total BMD Week 144, N=3, 4, 3, 10	0.0340 (± 0.02524)	0.0923 (± 0.07682)	0.0933 (± 0.04150)	0.0751 (± 0.05741)
Hip Total BMD Week 192, N=2, 4, 3, 9	0.0135 (± 0.00919)	0.0983 (± 0.10856)	0.0563 (± 0.07100)	0.0654 (± 0.08327)
Hip Total BMD Week 240, N=2, 3, 3, 8	0.0115 (± 0.02192)	0.1137 (± 0.05701)	-0.0073 (± 0.06178)	0.0428 (± 0.07481)
Hip Total BMD Week 288, N=0, 1, 0, 1	0.0 (± 0.0)	-0.0200 (± 0.0)	0.0 (± 0.0)	-0.0200 (± 0.0)
Hip Total BMD LOE, N=4, 5, 4, 13	-0.0115 (± 0.03899)	0.0658 (± 0.07776)	0.0207 (± 0.07549)	0.0282 (± 0.07038)
Lumbar Spine BMD Week 48, N=1, 1, 5, 7	0.0480 (± 0.0)	0.0590 (± 0.0)	0.0914 (± 0.05647)	0.0806 (± 0.04978)

Lumbar Spine BMD Week 96, N=7, 5, 4, 16	0.0414 (± 0.05230)	0.0554 (± 0.04271)	0.1158 (± 0.08060)	0.0644 (± 0.06210)
Lumbar Spine BMD Week 144, N=5, 5, 4, 14	0.0200 (± 0.06257)	0.0850 (± 0.05323)	0.1138 (± 0.05734)	0.0700 (± 0.06688)
Lumbar Spine BMD Week 192, N=5, 5, 4, 14	0.0554 (± 0.13220)	0.0766 (± 0.04180)	0.1123 (± 0.05197)	0.0792 (± 0.08423)
Lumbar Spine BMD Week 240, N=5, 4, 4, 13	0.0750 (± 0.14168)	0.0455 (± 0.04107)	0.1027 (± 0.04786)	0.0745 (± 0.09073)
Lumbar Spine BMD Week 288, N=1, 1, 0, 2	0.1860 (± 0.0)	0.0700 (± 0.0)	0.0 (± 0.0)	0.1280 (± 0.08202)
Lumbar Spine BMD LOE, N=7, 5, 5, 17	0.0737 (± 0.11346)	0.0492 (± 0.04649)	0.1194 (± 0.04999)	0.0799 (± 0.08241)
Whole Body BMD Week 48, N=1, 1, 5, 7	0.0050 (± 0.0)	0.0090 (± 0.0)	0.0178 (± 0.05277)	0.0147 (± 0.04342)
Whole Body BMD Week 96, N=7, 5, 4, 16	-0.0103 (± 0.03523)	-0.0100 (± 0.04136)	0.0230 (± 0.04872)	-0.0019 (± 0.04059)
Whole Body BMD Week 144, N=5, 5, 4, 14	-0.0250 (± 0.03662)	-0.0278 (± 0.05823)	-0.0060 (± 0.04721)	-0.0206 (± 0.04542)
Whole Body BMD Week 192, N=5, 5, 4, 14	-0.0532 (± 0.02477)	-0.0220 (± 0.07088)	-0.0212 (± 0.06209)	-0.0329 (± 0.05358)
Whole Body BMD Week 240, N=5, 4, 4, 13	-0.0426 (± 0.05601)	-0.0122 (± 0.08610)	-0.0493 (± 0.06965)	-0.0353 (± 0.06615)
Whole Body BMD Week 288, N=1, 1, 0, 2	-0.1140 (± 0.0)	-0.0710 (± 0.0)	0.0 (± 0.0)	-0.0925 (± 0.03041)
Whole Body BMD LOE, N=7, 5, 5, 17	-0.0501 (± 0.07360)	-0.0298 (± 0.08785)	-0.0224 (± 0.05773)	-0.0360 (± 0.07036)

Notes:

[22] - "0.0" entered for arithmetic mean for no data and for standard deviation when number (N) = 1.

[23] - "0.0" entered for arithmetic mean for no data and for standard deviation when number (N) = 1.

[24] - "0.0" entered for arithmetic mean for no data and for standard deviation when number (N) = 1.

[25] - "0.0" entered for arithmetic mean for no data and for standard deviation when number (N) = 1.

Statistical analyses

No statistical analyses for this end point

Secondary: Change In Walking Ability As Measured By The Six-Minute Walk Test (6MWT) To Week 24

End point title	Change In Walking Ability As Measured By The Six-Minute Walk Test (6MWT) To Week 24
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End point description:

The patient was instructed to walk the length of a pre-measured hallway for 6 minutes. The primary measurement was distance walked (in meters). The N of patients evaluated for the various time points differ from the total number of patients in the group. The N of patients evaluated is reported in the Category Title.

End point type	Secondary
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End point timeframe:

Baseline, Week 24 (primary treatment period)

End point values	0.3 mg/kg Asfotase Alfa (Primary Treatment)	0.5 mg/kg Asfotase Alfa (Primary Treatment)	Concurrent Control (Primary Treatment)	Asfotase Alfa Combined (Primary Treatment)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	7	6	6	13
Units: meters				
arithmetic mean (standard deviation)				
Change from Baseline to Week 24, N=7, 6, 4, 13	64.7 (± 73.04)	43.5 (± 43.18)	13.5 (± 69.77)	54.9 (± 59.71)

Statistical analyses

Statistical analysis title	Walking Ability Change From Baseline To Week 24
Statistical analysis description: Change From Baseline to Week 24 in Walking Ability as Measured by the 6MWT	
Comparison groups	Concurrent Control (Primary Treatment) v Asfotase Alfa Combined (Primary Treatment)
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority ^[26]
P-value	= 0.1303 ^[27]
Method	Wilcoxon rank-sum
Confidence interval	
level	95 %
sides	2-sided
lower limit	-73
upper limit	114

Notes:

[26] - The Hodges-Lehman-Sen estimate = 44.0.

[27] - Two-sided with p-value threshold <0.05 for statistical significance

Secondary: Change In Walking Ability As Measured By The 6MWT To Last Overall Exposure (LOE)

End point title	Change In Walking Ability As Measured By The 6MWT To Last Overall Exposure (LOE)
End point description: The patient was instructed to walk the length of a pre-measured hallway for 6 minutes. The primary measurement was distance walked (in meters). The N of patients evaluated for the various time points differ from the total number of patients in the group. The N of patients evaluated is reported in the Category Title.	
End point type	Secondary
End point timeframe: Baseline, up to 288 weeks of asfotase alfa exposure, including LOE	

End point values	0.3 mg/kg Asfotase Alfa (Primary Treatment)	0.5 mg/kg Asfotase Alfa (Primary Treatment)	Concurrent Control (Primary Treatment)	Asfotase Alfa Combined (Primary Treatment)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	7	6	6	19
Units: meters				
arithmetic mean (standard deviation)				
Change from Baseline LOE, N=7, 6, 5, 18	89.4 (± 81.32)	2.2 (± 121.79)	74.4 (± 107.40)	56.2 (± 104.85)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In HPP-related Osteomalacia As Measured By Trans-iliac Crest Bone Biopsy: Osteoid Volume/Bone Volume

End point title	Change From Baseline In HPP-related Osteomalacia As Measured By Trans-iliac Crest Bone Biopsy: Osteoid Volume/Bone Volume
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End point description:

A trans-iliac crest bone biopsy was performed to quantify changes from Baseline in histomorphometric parameters relevant for evaluation of osteomalacia severity, including Osteoid Volume/Bone Volume (%). The difference in time under observation between asfotase alfa groups (Week 48) and control group (Week 24) resulted from study design. Control patients did not receive active treatment for the first 24 weeks, and were not on active treatment when bone biopsy assessments were performed. The N of patients evaluated differs from the total number of patients in the group. The N of patients evaluated is reported in the Category Title.

End point type	Secondary
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End point timeframe:

Baseline, Week 24 (Control group), and Week 48 (Asfotase alfa groups)

End point values	0.3 mg/kg Asfotase Alfa (Primary Treatment)	0.5 mg/kg Asfotase Alfa (Primary Treatment)	Concurrent Control (Primary Treatment)	Asfotase Alfa Combined (Primary Treatment)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	7	6	6	13
Units: percentage of volume				
arithmetic mean (standard deviation)				
Change from Baseline, N=6, 6, 6, 12	1.213 (± 3.2488)	-2.845 (± 2.3769)	0.200 (± 4.7679)	-0.816 (± 3.4434)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In HPP-related Osteomalacia As Measured By Trans-iliac Crest Bone Biopsy: Osteoid Thickness

End point title	Change From Baseline In HPP-related Osteomalacia As Measured By Trans-iliac Crest Bone Biopsy: Osteoid Thickness
End point description:	
A trans-iliac crest bone biopsy was performed to quantify changes from Baseline in histomorphometric parameters relevant for evaluation of osteomalacia severity, including Osteoid Thickness (micrometers [um]). The difference in time under observation between asfotase alfa groups (Week 48) and control group (Week 24) resulted from study design. Control patients did not receive active treatment for the first 24 weeks, and were not on active treatment when bone biopsy assessments were performed. The N of patients evaluated differs from the total number of patients in the group. The N of patients evaluated is reported in the Category Title.	
End point type	Secondary
End point timeframe:	
Baseline, Week 24 (Control group), and Week 48 (Asfotase alfa groups)	

End point values	0.3 mg/kg Asfotase Alfa (Primary Treatment)	0.5 mg/kg Asfotase Alfa (Primary Treatment)	Concurrent Control (Primary Treatment)	Asfotase Alfa Combined (Primary Treatment)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	7	6	6	13
Units: um				
arithmetic mean (standard deviation)				
Change from Baseline, N=6, 6, 6, 12	-0.013 (± 3.6333)	-1.516 (± 2.3556)	-1.132 (± 6.0884)	-0.764 (± 3.0229)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In HPP-related Osteomalacia As Measured By Trans-iliac Crest Bone Biopsy: Mineralization Lag Time

End point title	Change From Baseline In HPP-related Osteomalacia As Measured By Trans-iliac Crest Bone Biopsy: Mineralization Lag Time
End point description:	
A trans-iliac crest bone biopsy was performed to quantify changes from Baseline in histomorphometric parameters relevant for evaluation of osteomalacia severity, including Mineralization Lag Time (days). The difference in time under observation between asfotase alfa groups (Week 48) and control group (Week 24) resulted from study design. Control patients did not receive active treatment for the first 24 weeks, and were not on active treatment when bone biopsy assessments were performed. The N of patients evaluated differs from the total number of patients in the group. The N of patients evaluated is reported in the Category Title.	
End point type	Secondary
End point timeframe:	
Baseline, Week 24 (Control group), and Week 48 (Asfotase alfa groups)	

End point values	0.3 mg/kg Asfotase Alfa (Primary Treatment)	0.5 mg/kg Asfotase Alfa (Primary Treatment)	Concurrent Control (Primary Treatment)	Asfotase Alfa Combined (Primary Treatment)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	7	6	6	13
Units: days				
arithmetic mean (standard deviation)				
Change from Baseline, N=4, 5, 5, 9	-908.255 (± 1313.6158)	-126.946 (± 142.2929)	78.296 (± 167.0895)	-474.195 (± 909.2779)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

up to 288 weeks

Adverse event reporting additional description:

Only adverse events with an onset date are included in the cumulative exposure category.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	13.0
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Reporting groups

Reporting group title	0.3 mg/kg Asfotase Alfa (Primary Treatment)
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Reporting group description:

Asfotase alfa Cohort 1: Daily SC injections of 0.3 mg/kg asfotase alfa (2.1 mg/kg/week total)

Reporting group title	0.5 mg/kg Asfotase Alfa (Primary Treatment)
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Reporting group description:

Asfotase alfa Cohort 2: Daily SC injections of 0.5 mg/kg asfotase alfa (3.5 mg/kg/week total)

Reporting group title	Concurrent Control (Primary Treatment)
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Reporting group description:

No asfotase alfa treatment during primary treatment period: first 24 weeks.

After 24 weeks, Control Group patients were eligible to begin asfotase alfa treatment in the open-label extension treatment period.

Reporting group title	Asfotase Alfa Combined (Extension Treatment)
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Reporting group description:

Adverse events occurring in patients from Cohort 1, Cohort 2, and original Control group during exposure to asfotase alfa.

Serious adverse events	0.3 mg/kg Asfotase Alfa (Primary Treatment)	0.5 mg/kg Asfotase Alfa (Primary Treatment)	Concurrent Control (Primary Treatment)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	2 / 6 (33.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adrenal adenoma			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Arnold-Chiari malformation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial pressure increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device dislocation			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injection site hypersensitivity			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Tympanic membrane perforation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactoid reaction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoaesthesia oral			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterovirus infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal abscess			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Asfotase Alfa Combined (Extension Treatment)		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 19 (47.37%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adrenal adenoma			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Arnold-Chiari malformation			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Convulsion			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Intracranial pressure increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Device dislocation			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injection site hypersensitivity			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Tympanic membrane perforation			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactoid reaction			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoaesthesia oral			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Abscess			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocarditis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enterovirus infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Staphylococcal abscess			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Staphylococcal infection			
subjects affected / exposed	1 / 19 (5.26%)		
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	0.3 mg/kg Asfotase Alfa (Primary Treatment)	0.5 mg/kg Asfotase Alfa (Primary Treatment)	Concurrent Control (Primary Treatment)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	6 / 6 (100.00%)	6 / 6 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign renal neoplasm			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Lipoma subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Lung neoplasm subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Melanocytic naevus subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 6	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Uterine leiomyoma subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Surgical and medical procedures Colon polypectomy subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Axillary pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Catheter site inflammation subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Catheter site erythema subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Cyst			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Device failure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Facial pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	0 / 7 (0.00%)	3 / 6 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	5	0
Feeling abnormal			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Fibrosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gait disturbance			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injection site atrophy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injection site discolouration			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	9	0	0
Injection site erythema			
subjects affected / exposed	3 / 7 (42.86%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	61	5	0
Injection site exfoliation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injection site haematoma			
subjects affected / exposed	3 / 7 (42.86%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	14	6	0
Injection site haemorrhage			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injection site hypertrophy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injection site induration			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Injection site inflammation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injection site macule			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injection site mass			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injection site nodule			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injection site pain			
subjects affected / exposed	4 / 7 (57.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	20	0	0
Injection site papule			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Injection site pruritus			
subjects affected / exposed	3 / 7 (42.86%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	16	0	0
Injection site reaction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injection site scar			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injection site swelling			

subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	10	0	0
Injection site vesicles			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injection site warmth			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Local swelling			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Malaise			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Medical device pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Oedema peripheral			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	7	1	0
Pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Food allergy			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Immunisation reaction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Seasonal allergy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Reproductive system and breast disorders			
Breast calcifications			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Breast mass			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dysmenorrhea			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Ovarian cyst			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pelvic pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Spermatocele			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vaginal haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Bronchial hyperreactivity			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Dry throat			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Emphysema			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypoxia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Oropharyngeal pain			
subjects affected / exposed	2 / 7 (28.57%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	2	2	0
Respiratory disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Respiratory tract congestion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Rhinorrhoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Sinus congestion			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Sleep apnoea syndrome			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Initial insomnia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Insomnia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Intentional self-injury			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nightmare			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Sleep disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood 25-hydroxycholecalciferol increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood parathyroid hormone increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Blood pressure increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Blood human chorionic gonadotropin abnormal			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Haemoglobin decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Heart rate decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Heart rate increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Neutrophil count increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Physical examination abnormal			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Red blood cells urine			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ultrasound kidney abnormal			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vitamin D decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Weight increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
White blood cell count increased			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Arthropod bite			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Excoriation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Femur fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Fibula fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Foot fracture			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Hand fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ilium fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Joint dislocation			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Joint injury			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Joint sprain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Limb injury			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Meniscus lesion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Post procedural swelling			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Post-traumatic pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Procedural nausea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Procedural pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	2	3
Procedural vomiting			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Radius fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Thoracic vertebral fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tibia fracture			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tooth fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ulna fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Upper limb fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Wound			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Dizziness exertional			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Dysgeusia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	2 / 7 (28.57%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	4	1	1
Hypoaesthesia			

subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Intracranial pressure increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Loss of consciousness			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Migraine			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Neuralgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Neuropathy peripheral			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Post-traumatic headache			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Sinus headache			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Burning sensation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Cerumen impaction			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ear discomfort			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Ear pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ear pruritus			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Tinnitus			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tympanic membrane disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tympanic membrane perforation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vertigo			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Blepharitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Cataract			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Conjunctival deposit			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Conjunctival discolouration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Conjunctival disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Corneal deposits			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Deposit eye			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dry eye			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eye irritation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eyelid disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Keratopathy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Lacrimation increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Optic atrophy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Photopsia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Punctate keratitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Vitreous detachment subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Abdominal hernia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Abdominal mass subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Colitis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Colonic polyp subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Constipation subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Dental caries subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 6 (16.67%) 2	0 / 6 (0.00%) 0
Dyspepsia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Dysphagia			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastroesophageal reflux disease			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal motility disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gingival hypertrophy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gingival swelling			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gingivitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hyperchlorhydria			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Irritable bowel syndrome			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Loose tooth			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	2	1	2
Tooth disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tooth loss			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Actinic keratosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blister			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dermal cyst			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Dermatitis contact			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dermatitis diaper			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	8	0	0
Excessive skin			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ingrowing nail			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Ingrown hair			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Onychalgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Onychomadesis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Photodermatitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rash macular			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Rash papular			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Scar			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Skin discolouration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin hyperpigmentation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin lesion			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Renal and urinary disorders			
Bladder pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Haematuria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nephrocalcinosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nephrolithiasis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Renal cyst			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Renal pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypothyroidism			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 7 (28.57%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	6	3	2
Arthritis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Arthropathy			

subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Back pain			
subjects affected / exposed	2 / 7 (28.57%)	3 / 6 (50.00%)	1 / 6 (16.67%)
occurrences (all)	3	3	3
Bone pain			
subjects affected / exposed	1 / 7 (14.29%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	3	2	0
Bursitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Chondrocalcinosis pyrophosphate			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Deformity thorax			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Flank pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Jaw disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Joint range of motion decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Joint stiffness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Joint swelling			
subjects affected / exposed	2 / 7 (28.57%)	3 / 6 (50.00%)	0 / 6 (0.00%)
occurrences (all)	7	3	0
Joint warmth			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Lower extremity mass			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Metatarsalgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Muscular weakness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	4
Musculoskeletal disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Musculoskeletal stiffness			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	3
Myalgia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Neck pain			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Nodule on extremity			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	4	0
Osteoarthritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			

subjects affected / exposed	2 / 7 (28.57%)	3 / 6 (50.00%)	1 / 6 (16.67%)
occurrences (all)	13	7	1
Sacroiliitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Spinal disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tendon disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Tendon pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Tendonitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Trigger finger			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Wrist deformity			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Acute sinusitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Adenovirus infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Bronchiolitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Cellulitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis bacterial			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Diarrhoea infectious			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Diverticulitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Ear infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Endocarditis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Gastroenteritis viral			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Herpes zoster			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Nasopharyngitis			
subjects affected / exposed	0 / 7 (0.00%)	2 / 6 (33.33%)	2 / 6 (33.33%)
occurrences (all)	0	2	2
Oral candidiasis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Otitis media			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Paronychia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Post procedural infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Sinusitis			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Staphylococcal abscess			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Staphylococcal infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Staphylococcal skin infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Tinea cruris			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tinea pedis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Tooth infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Tinea infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Upper Respiratory tract infection			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vaginitis bacterial			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Viral infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Viral pharyngitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Gout			

subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0

Non-serious adverse events	Asfotase Alfa Combined (Extension Treatment)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 19 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign renal neoplasm			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Lipoma			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Lung neoplasm			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Melanocytic naevus			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Uterine leiomyoma			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Surgical and medical procedures			
Colon polypectomy			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Axillary pain			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Catheter site inflammation			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	17		
Catheter site erythema			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Cyst			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Device failure			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Facial pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	7		
Feeling abnormal			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Fibrosis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Gait disturbance			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Injection site atrophy			
subjects affected / exposed	5 / 19 (26.32%)		
occurrences (all)	8		
Injection site discolouration			
subjects affected / exposed	9 / 19 (47.37%)		
occurrences (all)	66		
Injection site erythema			

subjects affected / exposed	13 / 19 (68.42%)		
occurrences (all)	121		
Injection site exfoliation			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Injection site haematoma			
subjects affected / exposed	10 / 19 (52.63%)		
occurrences (all)	33		
Injection site haemorrhage			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Injection site hypertrophy			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	12		
Injection site induration			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	4		
Injection site inflammation			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Injection site macule			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	10		
Injection site mass			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	5		
Injection site nodule			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Injection site pain			
subjects affected / exposed	6 / 19 (31.58%)		
occurrences (all)	26		
Injection site papule			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Injection site pruritus			

subjects affected / exposed	5 / 19 (26.32%)		
occurrences (all)	20		
Injection site reaction			
subjects affected / exposed	7 / 19 (36.84%)		
occurrences (all)	56		
Injection site scar			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Injection site swelling			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	12		
Injection site vesicles			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Injection site warmth			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	3		
Local swelling			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Medical device pain			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Oedema peripheral			
subjects affected / exposed	8 / 19 (42.11%)		
occurrences (all)	16		
Pain			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	4		
Pyrexia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Immune system disorders			

Food allergy			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Immunisation reaction			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Seasonal allergy			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Reproductive system and breast disorders			
Breast calcifications			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Breast mass			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Dysmenorrhea			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	8		
Ovarian cyst			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Pelvic pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Spermatocele			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Vaginal haemorrhage			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Bronchial hyperreactivity			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	5 / 19 (26.32%)		
occurrences (all)	6		
Dry throat			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Emphysema			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Hypoxia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Nasal congestion			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Oropharyngeal pain			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	5		
Respiratory disorder			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Respiratory tract congestion			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Sinus congestion			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Sleep apnoea syndrome			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Psychiatric disorders			

Anxiety			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Initial insomnia			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Insomnia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Intentional self-injury			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Nightmare			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Sleep disorder			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	3		
Blood 25-hydroxycholecalciferol increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Blood parathyroid hormone increased			

subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	3		
Blood pressure increased			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Blood human chorionic gonadotropin abnormal			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Haemoglobin decreased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Heart rate decreased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Heart rate increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Lymphocyte count decreased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Neutrophil count increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Physical examination abnormal			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Red blood cells urine			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Ultrasound kidney abnormal			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Vitamin D decreased			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Weight increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	3		
White blood cell count increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Arthropod bite			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	4		
Contusion			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	4		
Excoriation			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Fall			
subjects affected / exposed	5 / 19 (26.32%)		
occurrences (all)	8		
Femur fracture			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Fibula fracture			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Foot fracture			

subjects affected / exposed	7 / 19 (36.84%)		
occurrences (all)	10		
Hand fracture			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Ilium fracture			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Joint dislocation			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Joint injury			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	3		
Joint sprain			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	3		
Limb injury			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Meniscus lesion			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Post procedural swelling			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Post-traumatic pain			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	4		
Procedural nausea			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Procedural pain			
subjects affected / exposed	5 / 19 (26.32%)		
occurrences (all)	11		
Procedural vomiting			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Radius fracture			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Thoracic vertebral fracture			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Tibia fracture			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	3		
Tooth fracture			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Ulna fracture			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Upper limb fracture			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Wound			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Nervous system disorders			
Balance disorder			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	7 / 19 (36.84%)		
occurrences (all)	7		
Dizziness exertional			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Dysgeusia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	5 / 19 (26.32%)		
occurrences (all)	28		
Hypoaesthesia			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	5		
Intracranial pressure increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Loss of consciousness			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Migraine			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	5		
Neuralgia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Neuropathy peripheral			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	9		
Post-traumatic headache			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Sinus headache			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Burning sensation			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Ear discomfort			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Ear pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Ear pruritus			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Tinnitus			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Tympanic membrane disorder			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Tympanic membrane perforation			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Vertigo			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Eye disorders			
Blepharitis			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Cataract			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Conjunctival deposit			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Conjunctival discolouration			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Conjunctival disorder			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Conjunctivitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Corneal deposits			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Deposit eye			
subjects affected / exposed	7 / 19 (36.84%)		
occurrences (all)	8		
Dry eye			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Eye irritation			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Eyelid disorder			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Keratopathy			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Lacrimation increased			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Optic atrophy			

subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Photopsia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Punctate keratitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Vitreous detachment			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	3		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Abdominal hernia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Abdominal mass			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Abdominal pain upper			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	6		
Colitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Colonic polyp			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	4		
Dental caries			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		

Diarrhoea			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	3		
Dyspepsia			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	3		
Dysphagia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Gastroesophageal reflux disease			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Gastrointestinal motility disorder			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Gingival hypertrophy			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Gingival swelling			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Gingivitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Hyperchlorhydria			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Irritable bowel syndrome			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Loose tooth			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		

Nausea subjects affected / exposed occurrences (all)	4 / 19 (21.05%) 7		
Tooth disorder subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 2		
Tooth loss subjects affected / exposed occurrences (all)	3 / 19 (15.79%) 3		
Vomiting subjects affected / exposed occurrences (all)	2 / 19 (10.53%) 2		
Hepatobiliary disorders Hepatic steatosis subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Actinic keratosis subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Blister subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Dermal cyst subjects affected / exposed occurrences (all)	2 / 19 (10.53%) 2		
Dermatitis contact subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Dermatitis diaper subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 2		
Dry skin			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	8		
Excessive skin			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Ingrowing nail			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	3		
Ingrown hair			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Onychalgia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Onychomadesis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Photodermatosis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Rash macular			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	4		
Rash papular			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Scar			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Skin discolouration			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Skin hyperpigmentation			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Skin lesion			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Renal and urinary disorders			
Bladder pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Haematuria			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	3		
Nephrocalcinosis			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Nephrolithiasis			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	3		
Renal cyst			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Renal pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Hypothyroidism			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	13 / 19 (68.42%)		
occurrences (all)	41		
Arthritis			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Arthropathy			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	10 / 19 (52.63%)		
occurrences (all)	14		
Bone pain			
subjects affected / exposed	9 / 19 (47.37%)		
occurrences (all)	14		
Bursitis			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	3		
Chondrocalcinosis pyrophosphate			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Deformity thorax			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Flank pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Jaw disorder			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Joint range of motion decreased			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	3		
Joint stiffness			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		

Joint swelling			
subjects affected / exposed	7 / 19 (36.84%)		
occurrences (all)	16		
Joint warmth			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Lower extremity mass			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Metatarsalgia			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	7		
Muscle spasms			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	4		
Muscular weakness			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Musculoskeletal chest pain			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Musculoskeletal disorder			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	8 / 19 (42.11%)		
occurrences (all)	11		
Musculoskeletal stiffness			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	3		
Myalgia			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	4		
Neck pain			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	5		

Nodule on extremity			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	5		
Osteoarthritis			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	4		
Pain in extremity			
subjects affected / exposed	12 / 19 (63.16%)		
occurrences (all)	46		
Sacroiliitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Spinal disorder			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Tendon disorder			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Tendon pain			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Tendonitis			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	3		
Trigger finger			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Wrist deformity			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Infections and infestations			
Abscess			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Acute sinusitis			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Adenovirus infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Bronchiolitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Cellulitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Conjunctivitis bacterial			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Diarrhoea infectious			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Diverticulitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Ear infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Endocarditis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	3		
Gastroenteritis viral			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Gastrointestinal infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Herpes zoster			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Lower respiratory tract infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	6 / 19 (31.58%)		
occurrences (all)	8		
Oral candidiasis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Otitis media			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Paronychia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Post procedural infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Respiratory tract infection viral			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	5 / 19 (26.32%)		
occurrences (all)	20		
Staphylococcal abscess			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Staphylococcal infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Staphylococcal skin infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Tinea cruris			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Tinea pedis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Tooth infection			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	5		
Tinea infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Upper Respiratory tract infection			
subjects affected / exposed	7 / 19 (36.84%)		
occurrences (all)	22		
Urinary tract infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Vaginitis bacterial			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Viral infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Viral pharyngitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Viral upper respiratory tract infection			

subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Metabolism and nutrition disorders Gout subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 May 2010	<ul style="list-style-type: none">• Reference to pharmacodynamics was removed from the protocol title and overall study objectives. This change aligned with the primary objectives to assess the safety, efficacy, and pharmacokinetic (PK) of asfotase alfa.• Inclusion criteria for osteomalacia were changed from an osteoid surface z-score of at least + 2 on bone biopsy to an osteoid thickness (O.Th) and mineralization lag time (MLT) z score of + 2 or more, as these were determined to be the best parameters for assessing osteomalacia on bone biopsy (that is, mineralization defects). Additional nutritional assessments were added, including caloric and calcium intake.
01 September 2010	<ul style="list-style-type: none">• Reference to the absence of asfotase alfa antibodies in the patient population was removed due to detection of antibodies in some patients.• Language was changed to indicate that screening would continue until 18 adolescent and adult patients eligible for study participation and randomization were identified.• Language was changed to clarify the use of birth control by female patients of childbearing potential and sexually mature males, and the definition of "nonchildbearing female" was provided.• Pregnancy testing methods were modified to include urine sample testing at any time serum sample testing was performed.• Exclusion criterion on bisphosphonate use was changed to allow patients to enter the study who had not used bisphosphonates within the past 2 years, under the stipulation that their bone resorption marker assessments were within the normal range or elevated.• Language was added to clarify the flexibility of assessment scheduling, as long as the specified order of assessments and/or availability of results pertaining to assessments were maintained.• Language was added to clarify that the required radiographic images that needed to be collected at the Screening and Week 24 study visits, and to indicate that only those patients randomized to asfotase alfa treatment needed to undergo PK testing.• Required radiographic images to be collected at the Screening and Week 24 study visits were provided as follows: Screening: Lateral skull, lateral thoracic spine, lateral lumbar spine, posterior anterior (PA) hand/wrist (unilateral non-dominant), anteroposterior (AP) pelvis, AP bilateral femurs (femora), AP bilateral tibia/fibula, and bilateral AP feet.• Urinary calcium: creatinine ratio was changed from a safety evaluation to a disease biomarker evaluation. In addition, text was added to specify that a spot urine sample must be collected for this evaluation.

01 September 2010	<ul style="list-style-type: none"> • The definition of injection-associated reactions (IARs) was clarified to reflect that an IAR must represent a systemic sign/symptom/finding, be assessed as related to the study drug, and occur within 3 hours of drug administration. Notification of serious IARs was changed to be within 24 hours rather than 48 hours of the investigational site's first knowledge. Language was also added to more fully define ISRs and assist investigational sites in identifying them. Information was also added that explicitly detailed injection site reaction (ISR) data recording and reporting procedures. • A 12-lead electrocardiogram (ECG) assessment was added at Baseline and Week 24 as a routine safety measure to assess potential changes in cardiac function. • Language was added to reflect that both prior and concomitant medications and therapies taken by the patient were recorded if administered within 2 weeks prior to study entry. • Language was added to allow for the collection of fasting blood and urine samples for testing of the bone resorption markers serum C-telopeptide and urine N-telopeptide or urine deoxypyridinoline. This testing was added to the Screening visit to assess patients with a history of prior bisphosphonate use. • Tanner staging was added as an assessment for patients <18 years at time of study entry for the Baseline and Week 24 visits to assist in the analysis of functional endpoints. • The assessment of serum 25-hydroxy (25[OH]) vitamin D was changed from a safety evaluation to an "other" study evaluation. This evaluation was used to exclude patients with nutritional rickets and to assist in the evaluation of radiographic endpoints for the study, and it was not intended to be a routine safety measure. • Nutritional assessment was changed from a safety evaluation to an "other" study evaluation. This was primarily intended for purposes of evaluating caloric and calcium intake in relation to growth parameters.
01 September 2010	<ul style="list-style-type: none"> • A newly created section was added to reflect that medical monitoring responsibilities for the study were delegated to Premier Research. The scope of these responsibilities and relevant contact information were added. • Language describing the assessment of the safety and tolerability of SC injections of asfotase alfa was altered to demonstrate that the totality of safety information collected was examined when assessments were performed. • Language was added to distinguish enrolled patients from those who were confirmed as eligible for the study. • Language was added to clarify the required study assessments for patients randomized to receive asfotase alfa versus those receiving no treatment. • Language was added to reflect that IARs and ISRs were subsets of AEs.
10 December 2010	<ul style="list-style-type: none"> • The study methodology section was updated to reflect that the study was extended from 6 months to a total of 18 months. • Reference to osteoid thickness as an inclusion criterion was removed after examining data from ongoing studies that indicated MLT is a more relevant parameter. • Language was added to reflect that all patients who enrolled in the extension period would receive 0.5 mg/kg/day asfotase alfa (3.5 mg/kg/week) and to reflect the change in study duration. • Language was added to reflect the transition of no treatment group patients to active treatment. Patients from this group received training in the injection of asfotase alfa at the beginning of the extension period. • An additional transiliac crest bone biopsy was added at Week 72. Additional assessments, including skeletal radiographs, tooth loss, panorex radiographs, Dual-energy X-ray absorptiometry (DEXA) assessments, 6MWT, Lower Extremity Functional Scale (LEFS), Brief Pain Inventory-Short Form (BPI-SF), Bruininks-Oseretsky Test of Motor Proficiency, Second Edition (BOT-2), muscle strength assessment by handheld dynamometry (HHD), forced vital capacity (FVC) assessed by pulmonary function testing (PFT), and growth measurements (in adolescent patients only), were also added as described in the schedule of assessments. • Language was added to permit the continual assessment of dose/dosing schedule during the extension period and to reflect that the maximum allowable dose for all patients was 40 mg/day. • The number of eligible patients for the study was changed from 18 to 22 to account for screening failures. • Language was added to clarify the schedule/responsibilities of the home care nurse during the initial 4 weeks of home injections.

10 December 2010	<ul style="list-style-type: none"> • The statistical methods were modified and additional study visits were added to reflect the extension period timeline. • Language was updated to reflect the status of other asfotase alfa studies and listing the entire population of patients that have been exposed to this drug. • The term "ALPL" was replaced throughout the document with tissue-nonspecific alkaline phosphatase ("TNSALP") for consistency. • A new medical monitor was added to the study. Contact information was updated accordingly.
28 March 2011	<ul style="list-style-type: none"> • Language was clarified that the extension period of the study could extend out to regulatory approval of the drug. • The primary objective, in which a bone biopsy was analyzed for signs of osteomalacia, was moved to a secondary endpoint. Further research on osteomalacia indicated that bone changes in adults would be slower than in younger patients; therefore, a biopsy before 12 months was thought unlikely to show any effects of treatment. While a biopsy at 12 months was still performed in asfotase alfa patients, control patients had signed a consent allowing them to receive treatment after only 6 months. Lack of a 12-month control for osteomalacia prevented it from being a primary endpoint. • Reductions in inorganic pyrophosphate (PPi) and pyridoxal-5'-phosphate (PLP) were shifted from the secondary objectives to the primary objectives. • The efficacy, PK, pharmacodynamic (PD), safety, and other evaluations were updated to align with the revised objectives in the current protocol amendment. • Dose adjustment language was updated to increase flexibility and safety, allowing dose adjustments at any time during the study with input from the medical monitor. • Vital signs language was updated to align with other asfotase alfa protocols. • Knee flexors and extensors were added to the list of parameters assessed using handheld dynamometry (HHD) to bring the protocol in alignment with other asfotase alfa protocols. • Discontinuation of patient diaries, which collected data on treatment compliance.
20 October 2011	<ul style="list-style-type: none"> • Dosing of asfotase alfa was increased to 1 mg/kg/day, 6 days/week, after the first 6 months of the extension period. Rationale was also added for this adjustment: The highest dose given to adults was comparable to the lowest dose given to juveniles that had shown effectiveness. As a consequence of this change, the maximum daily dose was adjusted to 80 mg/day. • The End of Study visit language was modified to include all assessments scheduled every 6 months after Week 48. • Language in the introduction of the protocol was modified for consistency with the latest version of the Investigator's Brochure (IB). • The study medication description was updated to reflect the actual vial contents. • Safety officer information was updated.
14 October 2014	<ul style="list-style-type: none"> • Removed pulmonary function testing from the exploratory objectives. • Updated wording regarding dose adjustments for efficacy or safety reasons. • Added sampling for PK analysis to the extension period of the study, at all visits at which anti-asfotase alfa antibodies are being assessed. Antibody testing and PK analysis were performed at the same time to allow for evaluation of the impact of the antibodies on PK. • Full ophthalmology examinations (including funduscopy) were added to better characterize potential ectopic calcifications. • Changes to Data Monitoring Committee (DMC) operations (endorsed by the DMC) were made based on a new DMC charter (dated 10 January 2013) and Sponsor discussions on DMC stopping rules; ad hoc review and stopping rules are no longer required; however, the DMC must be notified immediately. • Changed testing requirements for IARs. • Medical monitor and drug safety physician information for study was updated 26 October 2015 • Updating of title page to current protocol cover page format. • Updating of site information for Alexion European office • Updating Medical Monitor information
26 October 2015	<ul style="list-style-type: none"> • Updating of title page to current protocol cover page format. • Updating of site information for Alexion European office • Updating Medical Monitor information

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported