Clinical trial results:
A Phase 2a Randomized, Multi-center, Open-Label, Pharmacokinetic, and Dose Response Study of Asfotase Alfa in Adult Patients with Pediatric-Onset Hypophosphatasia (HPP)

Summary

EudraCT number	2015-003131-35
Trial protocol	DE
Global end of trial date	21 June 2017

Results information

Result version number	v1 (current)
This version publication date	23 September 2018
First version publication date	23 September 2018

Trial information

Trial identification

Sponsor protocol code	AA-HPP-208

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02797821
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alexion Pharmaceuticals, Inc
Sponsor organisation address	100 College Street, New Haven CT, United States,
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)	No
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 June 2017
Global end of trial reached?	Yes
Global end of trial date	21 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of asfotase alfa following administration of a range of dose regimens that encompasses the dose proven to be effective in children (in adult participants with pediatric-onset hypophosphatasia [HPP]).

Protection of trial subjects:

This study was conducted in accordance with International Council for 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 February 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	United States: 14
Worldwide total number of subjects	27
EEA total number of subjects	13

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)	0
Adults (18-64 years)	24
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Twenty-seven participants were enrolled in this phase 2a study. Participants attended 4 study centres in 2 countries. The first participant was enrolled on 6 June 2016, and the last participant completed the study on 21 June 2017.

Pre-assignment

Screening details:

Participants with documented paediatric-onset HPP, defined as onset of first signs/symptoms of HPP prior to 18 years of age, were enrolled. Twenty-seven participants were randomised, 8 to the 0.5 milligram (mg)/kilogram (kg) cohort, 10 in the 2.0 mg/kg cohort, and 9 in the 3.0 mg/kg cohort. The first dose of asfotase alfa was given on Day 1, Week

Pre-assignment period milestones

Number of subjects started	27
Number of subjects completed	27

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Asfotase Alfa 0.5 mg/kg Dose

Arm description:

Participants received 0.5 mg/kg of asfotase alfa administered subcutaneously (SC) 3 times a week from Weeks 3 through 9 following the initial single dose on Day 1 in Week 1.

Arm type	Active comparator
Investigational medicinal product name	Asfotase Alfa 0.5 mg/kg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

After the initial single dose of Asfotase Alfa 0.5 mg/kg on Day 1, 3 doses were administered each week.

Arm title	Asfotase Alfa 2.0 mg/kg Dose

Arm description:

Participants received 2.0 mg/kg of asfotase alfa administered SC 3 times a week from Weeks 3 through 9 following the initial single dose on Day 1 in Week 1.

Arm type	Active comparator
Investigational medicinal product name	Asfotase Alfa 2.0 mg/kg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

After the initial single dose of Asfotase Alfa 2.0 mg/kg on Day 1, 3 doses were administered each week.

Arm title	Asfotase Alfa 3.0 mg/kg Dose

Arm description:

Participants received 3.0 mg/kg of asfotase alfa administered SC 3 times a week from Weeks 3 through 9 following the initial single dose on Day 1 in Week 1.

Arm type	Active comparator
Investigational medicinal product name	Asfotase Alfa 3.0 mg/kg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

After the initial single dose of Asfotase Alfa 3.0 mg/kg on Day 1, 3 doses were administered each week.

Number of subjects in period 1	Asfotase Alfa 0.5 mg/kg Dose	Asfotase Alfa 2.0 mg/kg Dose	Asfotase Alfa 3.0 mg/kg Dose
Started	8	10	9
Received at least 1 Dose of Study Drug	8	10	9
Completed	8	10	9

Baseline characteristics

Reporting groups	
Reporting group title	Asfotase Alfa 0.5 mg/kg Dose
Reporting group description:	
Participants received 0.5 mg/kg of asfotase alfa administered subcutaneously (SC) 3 times a week from Weeks 3 through 9 following the initial single dose on Day 1 in Week 1.	
Reporting group title	Asfotase Alfa 2.0 mg/kg Dose
Reporting group description:	
Participants received 2.0 mg/kg of asfotase alfa administered SC 3 times a week from Weeks 3 through 9 following the initial single dose on Day 1 in Week 1.	
Reporting group title	Asfotase Alfa 3.0 mg/kg Dose
Reporting group description:	
Participants received 3.0 mg/kg of asfotase alfa administered SC 3 times a week from Weeks 3 through 9 following the initial single dose on Day 1 in Week 1.	

Reporting group values	Asfotase Alfa 0.5 mg/kg Dose	Asfotase Alfa 2.0 mg/kg Dose	Asfotase Alfa 3.0 mg/kg Dose
Number of subjects	8	10	9
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	8	9	7
From 65-84 years	0	1	2
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	41.5	42.7	50
standard deviation	± 17.90	± 16.77	± 17.01
Gender categorical Units: Subjects			
Female	5	6	5
Male	3	4	4
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	0
Non Hispanic or Latino	8	10	9
Unknown or Not Reported	0	0	0
Race 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	10	9
More than one race	1	0	0
Unknown or Not Reported	0	0	0
Baseline Inorganic Pyrophosphate (PPi)			
Units: nanogram (ng)/millilitre (mL)			
arithmetic mean	5.4	5.3	5.0
standard deviation	± 1.64	± 1.22	± 0.86
Baseline Pyridoxal 5'-Phosphate (PLP)			
Units: nanogram (ng)/millilitre (mL)			
arithmetic mean	309.5	382.1	229.5
standard deviation	± 349.16	± 385.89	± 321.43

Reporting group values	Total		
Number of subjects	27		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	24		
From 65-84 years	3		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	16		
Male	11		
Ethnicity			
Units: Subjects			
Hispanic or Latino	0		
Non Hispanic or Latino	27		
Unknown or Not Reported	0		
Race			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	0		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	0		
White	26		
More than one race	1		
Unknown or Not Reported	0		

Baseline Inorganic Pyrophosphate (PPi) Units: nanogram (ng)/millilitre (mL) arithmetic mean standard deviation	- -		
Baseline Pyridoxal 5'-Phosphate (PLP) Units: nanogram (ng)/millilitre (mL) arithmetic mean standard deviation	- -		

Subject analysis sets	
Subject analysis set title	All participants
Subject analysis set type	Safety analysis
Subject analysis set description: All randomized participants	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description: All randomized participants who received ≥ 1 dose of study drug and had ≥ 1 pretreatment and ≥ 1 on-treatment PPi result.	

Reporting group values	All participants	Full Analysis Set (FAS)	
Number of subjects	27	27	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	24	24	
From 65-84 years	3	3	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	44.8	44.8	
standard deviation	± 16.94	± 16.94	
Gender categorical Units: Subjects			
Female	16	16	
Male	11	11	
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	
Non Hispanic or Latino	27	27	
Unknown or Not Reported	0	0	
Race Units: Subjects			
American Indian or Alaska Native	0	0	

Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	26	26	
More than one race	1	1	
Unknown or Not Reported	0	0	
Baseline Inorganic Pyrophosphate (PPi)			
Units: nanogram (ng)/millilitre (mL)			
arithmetic mean	5.2	5.2	
standard deviation	± 1.23	± 1.23	
Baseline Pyridoxal 5’-Phosphate (PLP)			
Units: nanogram (ng)/millilitre (mL)			
arithmetic mean	309.7	309.7	
standard deviation	± 346.99	± 346.99	

End points

End points reporting groups

Reporting group title	Asfotase Alfa 0.5 mg/kg Dose
Reporting group description:	
Participants received 0.5 mg/kg of asfotase alfa administered subcutaneously (SC) 3 times a week from Weeks 3 through 9 following the initial single dose on Day 1 in Week 1.	
Reporting group title	Asfotase Alfa 2.0 mg/kg Dose
Reporting group description:	
Participants received 2.0 mg/kg of asfotase alfa administered SC 3 times a week from Weeks 3 through 9 following the initial single dose on Day 1 in Week 1.	
Reporting group title	Asfotase Alfa 3.0 mg/kg Dose
Reporting group description:	
Participants received 3.0 mg/kg of asfotase alfa administered SC 3 times a week from Weeks 3 through 9 following the initial single dose on Day 1 in Week 1.	
Subject analysis set title	All participants
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomized participants	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomized participants who received ≥ 1 dose of study drug and had ≥ 1 pretreatment and ≥ 1 on-treatment PPi result.	

Primary: Change In Plasma PPi From Baseline To Pre-3rd Dose At Week 9

End point title	Change In Plasma PPi From Baseline To Pre-3rd Dose At Week 9
End point description:	
Plasma PPi concentrations were determined using a specific enzyme-catalyzed reaction with a radiolabelled marker in a 3-step process. Baseline plasma PPi values were calculated by averaging pre-dose values from samples collected during the Run-in Period at -168, -156, -24, -12, and 0 hours before Baseline. Week 9 plasma PPi values were calculated using blood samples collected before administration of the 3rd dose. The analysis was a restricted maximum likelihood (REML)-based repeated measures mixed model with treatment, visit, sex, Baseline PPi, Baseline weight group (≥ median versus < median), and study drug lot assignment as factors and an unstructured covariance structure for within-subject correlation. Per inclusion criteria, participants had to have had a Screening PPi concentration of ≥3.9 µM. Three participants (1 in each group) had Screening PPi concentrations of ≥3.9 micromolar (µM), but Baseline PPi values ranged between 3.5 to 3.8 µM.	
End point type	Primary
End point timeframe:	
Baseline to Week 9	

End point values	Asfotase Alfa 0.5 mg/kg Dose	Asfotase Alfa 2.0 mg/kg Dose	Asfotase Alfa 3.0 mg/kg Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	10	8	
Units: µM				
least squares mean (standard error)	-2.604 (± 0.2399)	-3.797 (± 0.1949)	-4.484 (± 0.2120)	

Statistical analyses

Statistical analysis title	Asfotase Alfa 0.5 mg/kg Dose, Asfotase Alfa 3.0 mg

Statistical analysis description:

A fixed sequence testing procedure was performed to compare the 3.0 mg/kg cohort with the 0.5 mg/kg cohort first. The hypothesis testing for the second comparison of the 2.0 mg/kg cohort compared with the 0.5 mg/kg cohort was only performed if the null hypothesis was rejected for the previous comparison at a significance level of 0.05 (p-value <0.05). The primary endpoint was met if the null hypothesis was rejected for both comparisons at a significance level of 0.05 (both p-values <0.05).

Comparison groups	Asfotase Alfa 0.5 mg/kg Dose v Asfotase Alfa 3.0 mg/kg Dose
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [1]
Method	REML
Parameter estimate	Least Squares (LS) Means Difference
Point estimate	-1.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.544
upper limit	-1.216

Notes:

[1] - REML-based repeated measures mixed model (treatment, visit, sex, Baseline PPi, Baseline weight group [≥median vs < median], and study drug lot assignment as factors) with an unstructured covariance structure for within-participant correlation.

Statistical analysis title	Asfotase Alfa 0.5 mg/kg Dose, Asfotase Alfa 2.0 mg

Statistical analysis description:

A fixed sequence testing procedure was performed to compare the 3.0 mg/kg cohort with the 0.5 mg/kg cohort first. The hypothesis testing for the second comparison of the 2.0 mg/kg cohort compared with the 0.5 mg/kg cohort was only performed if the null hypothesis was rejected for the first comparison at a significance level of 0.05 (p-value <0.05). The primary endpoint was met if the null hypothesis was rejected for both comparisons at a significance level of 0.05 (both p-values <0.05).

Comparison groups	Asfotase Alfa 0.5 mg/kg Dose v Asfotase Alfa 2.0 mg/kg Dose
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0008 [2]
Method	Restricted maximum likelihood-based
Parameter estimate	LS Means Difference
Point estimate	-1.193
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.805
upper limit	-0.581

Notes:

[2] - REML-based repeated measures mixed model (treatment, visit, sex, Baseline PPi, Baseline weight group [≥median vs < median], and study drug lot assignment as factors) with an unstructured covariance structure for within-participant correlation.

Secondary: Change In Plasma PLP From Baseline To Pre-3rd Dose At Week 9

End point title	Change In Plasma PLP From Baseline To Pre-3rd Dose At Week 9

End point description:

Plasma PLP was quantified using tandem liquid chromatography/mass spectrometry. Baseline plasma PLP values were calculated by averaging the pre-dose PLP values from blood samples collected during the Run-in Period at -168, -156, -24, -12, and 0 hours before Baseline. Week 9 PLP values were calculated using blood samples collected before the administration of the 3rd dose. The analysis was a REML-based repeated measures mixed model with treatment, visit, sex, Baseline PPi, Baseline weight group (≥ median versus < median), and study drug lot assignment as factors and an unstructured covariance structure for within- subject correlation.

End point type	Secondary

End point timeframe:

Baseline to Week 9

End point values	Asfotase Alfa 0.5 mg/kg Dose	Asfotase Alfa 2.0 mg/kg Dose	Asfotase Alfa 3.0 mg/kg Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	10	9	
Units: ng/mL				
least squares mean (standard error)	-303.955 (± 9.4075)	-333.447 (± 8.1486)	-338.002 (± 8.5145)	

Statistical analyses

Statistical analysis title	Asfotase Alfa 0.5 mg/kg Dose, Asfotase Alfa 3.0 mg
Comparison groups	Asfotase Alfa 0.5 mg/kg Dose v Asfotase Alfa 3.0 mg/kg Dose
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0128 [3]
Method	REML
Parameter estimate	LS Means Difference
Point estimate	-34.047
Confidence interval	
level	95 %
sides	2-sided
lower limit	-60.171
upper limit	-7.922

Notes:

[3] - REML-based repeated measures mixed model (treatment, visit, sex, Baseline PPi, Baseline weight group [≥ median versus < median], and study drug lot assignment as factors) with an unstructured covariance structure for within-participant correlation.

Statistical analysis title	Asfotase Alfa 0.5 mg/kg Dose, Asfotase Alfa 2.0 mg

Comparison groups	Asfotase Alfa 0.5 mg/kg Dose v Asfotase Alfa 2.0 mg/kg Dose
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0239 [4]
Method	REML
Parameter estimate	LS Means Difference
Point estimate	-29.492
Confidence interval	
level	95 %
sides	2-sided
lower limit	-54.723
upper limit	-4.261

Notes:

[4] - REML-based repeated measures mixed model (treatment, visit, sex, Baseline PPi, Baseline weight group [≥ median versus < median], and study drug lot assignment as factors) with an unstructured covariance structure for within-participant correlation.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were monitored continuously throughout the study, from the run-in period through the safety follow-up call, which occurred 90 days after the last dose of study drug.

Adverse event reporting additional description:

Results for AEs occurred in >5% of the overall Safety population. An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product, biologic, or medical device, which did not necessarily have a causal relationship with the asfotase alfa.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Asfotase Alfa 0.5 mg/kg Dose

Reporting group description:

Participants received 0.5 mg/kg of asfotase alfa administered SC 3 times a week from Weeks 3 through 9 following the initial single dose on Day 1 in Week 1.

Reporting group title	Asfotase Alfa 2.0 mg/kg Dose

Reporting group description:

Participants received 2.0 mg/kg of asfotase alfa administered SC 3 times a week 9 following the initial single dose on Day 1 in Week 1.

Reporting group title	Asfotase Alfa 3.0 mg/kg Dose

Reporting group description:

Participants received 3.0 mg/kg of asfotase alfa administered SC 3 times a week from Weeks 3 through 9 following the initial single dose on Day 1 in Week 1.

Serious adverse events	Asfotase Alfa 0.5 mg/kg Dose	Asfotase Alfa 2.0 mg/kg Dose	Asfotase Alfa 3.0 mg/kg Dose
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 9 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

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

Non-serious adverse events	Asfotase Alfa 0.5 mg/kg Dose	Asfotase Alfa 2.0 mg/kg Dose	Asfotase Alfa 3.0 mg/kg Dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)	10 / 10 (100.00%)	9 / 9 (100.00%)
Injury, poisoning and procedural complications			

Contusion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	3 / 9 (33.33%)
occurrences (all)	0	0	5
Laceration			
subjects affected / exposed	2 / 8 (25.00%)	0 / 10 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Disturbance in attention			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
Head discomfort			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
Headache			
subjects affected / exposed	3 / 8 (37.50%)	3 / 10 (30.00%)	5 / 9 (55.56%)
occurrences (all)	10	9	7
Hypersomnia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	1 / 9 (11.11%)
occurrences (all)	0	3	1
Paraesthesia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	4 / 9 (44.44%)
occurrences (all)	0	0	10
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 8 (37.50%)	4 / 10 (40.00%)	3 / 9 (33.33%)
occurrences (all)	9	11	5
Feeling hot			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	2 / 9 (22.22%)
occurrences (all)	0	1	2
Influenza like illness			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
Injection site bruising			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
Injection site discomfort			

subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Injection site erythema			
subjects affected / exposed	2 / 8 (25.00%)	3 / 10 (30.00%)	4 / 9 (44.44%)
occurrences (all)	4	4	4
Injection site haematoma			
subjects affected / exposed	2 / 8 (25.00%)	0 / 10 (0.00%)	0 / 9 (0.00%)
occurrences (all)	3	0	0
Injection site pain			
subjects affected / exposed	2 / 8 (25.00%)	1 / 10 (10.00%)	3 / 9 (33.33%)
occurrences (all)	2	2	4
Injection site reaction			
subjects affected / exposed	1 / 8 (12.50%)	3 / 10 (30.00%)	4 / 9 (44.44%)
occurrences (all)	4	21	68
Pain			
subjects affected / exposed	1 / 8 (12.50%)	2 / 10 (20.00%)	1 / 9 (11.11%)
occurrences (all)	1	3	2
Peripheral swelling			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Pyrexia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Flatulence			
subjects affected / exposed	0 / 8 (0.00%)	2 / 10 (20.00%)	0 / 9 (0.00%)
occurrences (all)	0	3	0
Nausea			
subjects affected / exposed	2 / 8 (25.00%)	1 / 10 (10.00%)	2 / 9 (22.22%)
occurrences (all)	3	2	2
Skin and subcutaneous tissue disorders			
Erythema			

subjects affected / exposed	2 / 8 (25.00%)	3 / 10 (30.00%)	1 / 9 (11.11%)
occurrences (all)	4	7	2
Pruritus			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	3 / 9 (33.33%)
occurrences (all)	0	1	3
Insomnia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	2 / 9 (22.22%)
occurrences (all)	1	1	2
Restlessness			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	1 / 9 (11.11%)
occurrences (all)	1	1	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 8 (25.00%)	4 / 10 (40.00%)	5 / 9 (55.56%)
occurrences (all)	13	12	15
Back pain			
subjects affected / exposed	4 / 8 (50.00%)	1 / 10 (10.00%)	2 / 9 (22.22%)
occurrences (all)	13	4	2
Bone pain			
subjects affected / exposed	2 / 8 (25.00%)	3 / 10 (30.00%)	2 / 9 (22.22%)
occurrences (all)	3	3	3
Musculoskeletal chest pain			
subjects affected / exposed	2 / 8 (25.00%)	0 / 10 (0.00%)	1 / 9 (11.11%)
occurrences (all)	2	0	1
Musculoskeletal pain			
subjects affected / exposed	3 / 8 (37.50%)	0 / 10 (0.00%)	1 / 9 (11.11%)
occurrences (all)	3	0	2
Myalgia			
subjects affected / exposed	2 / 8 (25.00%)	0 / 10 (0.00%)	1 / 9 (11.11%)
occurrences (all)	8	0	4
Neck pain			

subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	1 / 9 (11.11%)
occurrences (all)	0	3	1
Pain in extremity			
subjects affected / exposed	4 / 8 (50.00%)	5 / 10 (50.00%)	4 / 9 (44.44%)
occurrences (all)	17	11	10
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	1 / 8 (12.50%)	3 / 10 (30.00%)	1 / 9 (11.11%)
occurrences (all)	1	3	1
Viral upper respiratory tract infection			
subjects affected / exposed	4 / 8 (50.00%)	0 / 10 (0.00%)	0 / 9 (0.00%)
occurrences (all)	4	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported