Clinical trial results:
A Phase 2, Randomized, Double-Blind, Placebo-Controlled,Dose-Finding, Clinical Trial Evaluating the Efficacy and Safety of Obeticholic Acid in Subjects with Primary Sclerosing Cholangitis

Summary

EudraCT number	2014-002205-38
Trial protocol	IT
Global end of trial date	

Results information

Result version number	v1
This version publication date	23 March 2018
First version publication date	23 March 2018

Trial information

Trial identification

Sponsor protocol code	747-207

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02177136
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Intercept Pharmaceuticals, Inc
Sponsor organisation address	4760 Eastgate Mall, San Diego, United States, 92121
Public contact	Kimberly Fowler, Senior Director, Clinical Operations , Intercept Pharmaceuticals, Inc, kfowler@interceptpharma.com
Scientific contact	Christian Weyer, M.D., M.A.S. Executive Vice President, R&D , Intercept Pharmaceuticals, Inc, christian.weyer@interceptpharma.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	Interim
Date of interim/final analysis	07 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 March 2017
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effects of oebticholic acid (OCA) on the following in subjects with PSC:
- serum alkaline phosphatase (ALP)
- safety

Protection of trial subjects:

The study has been in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects have been also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 February 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	United States: 73
Worldwide total number of subjects	77
EEA total number of subjects	4

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)	72
From 65 to 84 years	5

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment started December 2014 and completed September 2016.

Pre-assignment

Screening details:

All subjects were required to undergo thorough screening procedures, to confirm they met the eligibility criteria, during the 30 day period preceding the first dose.

Period 1

Period 1 title	Double-blind phase (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	1.5 mg OCA Titrating to 3 mg OCA

Arm description:

Subjects randomized to 1.5 mg OCA will take 1.5 mg OCA daily for 12 weeks. If tolerated, the dose will be increased to 3 mg OCA daily for an additional 12 weeks.

Arm type	Experimental
Investigational medicinal product name	OCA
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects randomized to 1.5 mg OCA will take 1.5 mg OCA daily for 12 weeks. If tolerated, the dose will be increased to 3 mg OCA daily for an additional 12 weeks.

Arm title	5 mg OCA Titrating to 10 mg OCA

Arm description:

Subjects randomized to 5 mg OCA will take 5 mg OCA daily for 12 weeks. If tolerated, the dose will be increased to 10 mg OCA daily for an additional 12 weeks.

Arm type	Experimental
Investigational medicinal product name	OCA
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects randomized to 5 mg OCA will take 5 mg OCA daily for 12 weeks. If tolerated, the dose will be increased to 10 mg OCA daily for an additional 12 weeks.

Arm title	Placebo

Arm description:

Subjects randomized to placebo will take placebo daily for 24 weeks.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects randomized to placebo will take placebo daily for 24 weeks.

Number of subjects in period 1[1]	1.5 mg OCA Titrating to 3 mg OCA	5 mg OCA Titrating to 10 mg OCA	Placebo
Started	25	26	25
Completed	19	21	21
Not completed	6	5	4
Consent withdrawn by subject	2	-	-
Adverse event, non-fatal	4	5	3
Protocol deviation	-	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 77 subjects were randomly allocated to treatment with placebo, 1.5 mg OCA titrated to 3 mg or 5 mg OCA titrated to 10 mg; however, 1 subject did not receive treatment. Therefore, the subject disposition, baseline analyses and efficacy analyses are based on the Intent-to-Treat Population of 76 subjects.

Baseline characteristics

Reporting groups	
Reporting group title	1.5 mg OCA Titrating to 3 mg OCA
Reporting group description:	
Subjects randomized to 1.5 mg OCA will take 1.5 mg OCA daily for 12 weeks. If tolerated, the dose will be increased to 3 mg OCA daily for an additional 12 weeks.	
Reporting group title	5 mg OCA Titrating to 10 mg OCA
Reporting group description:	
Subjects randomized to 5 mg OCA will take 5 mg OCA daily for 12 weeks. If tolerated, the dose will be increased to 10 mg OCA daily for an additional 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Subjects randomized to placebo will take placebo daily for 24 weeks.	

Reporting group values	1.5 mg OCA Titrating to 3 mg OCA	5 mg OCA Titrating to 10 mg OCA	Placebo
Number of subjects	25	26	25
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)	24	23	24
From 65-84 years	1	3	1
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	41.6	44.9	43.7
standard deviation	± 12.56	± 14.28	± 13.05
Gender categorical Units: Subjects			
Female	10	14	11
Male	15	12	14
Ethnicity Units: Subjects			
Hispanic or Latino	2	2	1
Not Hispanic or Latino	23	24	24
Race Units: Subjects			
Asian	1	0	0
Black or african American	3	4	3
White	21	22	22

Alkaline phosphatase (ALP) Units: U/L			
arithmetic mean	422.5	428.5	562.8
standard deviation	± 123.07	± 178.19	± 300.22
Total bilirubin Units: umol/L			
arithmetic mean	16.3	19.4	20.9
standard deviation	± 8.17	± 10.94	± 11.48
Weight Units: kg			
arithmetic mean	74.5	73.6	73.0
standard deviation	± 12.51	± 12.76	± 12.95
Height Units: cm			
arithmetic mean	174.4	170.4	172.6
standard deviation	± 8.95	± 11.61	± 10.70
BMI Units: kg/m2			
arithmetic mean	24.6	25.3	24.5
standard deviation	± 4.38	± 3.74	± 3.71
International Normalized ratio (INR) Units: n/a			
arithmetic mean	1.0	1.0	1.0
standard deviation	± 0.06	± 0.10	± 0.07

Reporting group values	Total		
Number of subjects	76		
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)	71		
From 65-84 years	5		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	35		
Male	41		
Ethnicity Units: Subjects			
Hispanic or Latino	5		
Not Hispanic or Latino	71		

Race Units: Subjects			
Asian	1		
Black or african American	10		
White	65		
Alkaline phosphatase (ALP) Units: U/L arithmetic mean standard deviation	- -		
Total bilirubin Units: umol/L arithmetic mean standard deviation	- -		
Weight Units: kg arithmetic mean standard deviation	- -		
Height Units: cm arithmetic mean standard deviation	- -		
BMI Units: kg/m2 arithmetic mean standard deviation	- -		
International Normalized ratio (INR) Units: n/a arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	1.5 mg OCA Titrating to 3 mg OCA
Reporting group description:	
Subjects randomized to 1.5 mg OCA will take 1.5 mg OCA daily for 12 weeks. If tolerated, the dose will be increased to 3 mg OCA daily for an additional 12 weeks.	
Reporting group title	5 mg OCA Titrating to 10 mg OCA
Reporting group description:	
Subjects randomized to 5 mg OCA will take 5 mg OCA daily for 12 weeks. If tolerated, the dose will be increased to 10 mg OCA daily for an additional 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Subjects randomized to placebo will take placebo daily for 24 weeks.	

Primary: Week 24 Change from Baseline in ALP

End point title	Week 24 Change from Baseline in ALP
End point description:	
The primary efficacy analysis will compare the Week 24 change from Baseline in ALP between OCA treatment group and placebo using an analysis of covariance (ANCOVA) model with fixed effects for treatment group and randomization strata, and Baseline as a covariate.	
End point type	Primary
End point timeframe:	
24 weeks	

End point values	1.5 mg OCA Titrating to 3 mg OCA	5 mg OCA Titrating to 10 mg OCA	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	26	25	
Units: U/L				
least squares mean (standard error)	-105.05 (± 38.02)	-110.19 (± 33.77)	-26.76 (± 36.65)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
The primary efficacy analysis will compare the Week 24 change from Baseline in ALP between OCA treatment group and placebo using an analysis of covariance (ANCOVA) model with fixed effects for treatment group and randomization strata, and Baseline as a covariate.	
Comparison groups	Placebo v 5 mg OCA Titrating to 10 mg OCA

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0434
Method	ANCOVA

Statistical analysis title	Statistical analysis 2
Comparison groups	1.5 mg OCA Titrating to 3 mg OCA v Placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0665
Method	ANCOVA

Secondary: Week 24 Change from baseline in alanine transaminase (ALT)

End point title	Week 24 Change from baseline in alanine transaminase (ALT)

End point description:

End point type	Secondary

End point timeframe:

24 weeks

End point values	1.5 mg OCA Titrating to 3 mg OCA	5 mg OCA Titrating to 10 mg OCA	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	26	25	
Units: U/L				
median (inter-quartile range (Q1-Q3))	-33.0 (-50.5 to 5)	-5.5 (-30.0 to 4.5)	-19.5 (-49.0 to 4.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Week 24 Change from Baseline in aspartate aminotransferase (AST)

End point title	Week 24 Change from Baseline in aspartate aminotransferase (AST)

End point description:

End point type	Secondary

End point timeframe:
24 weeks

End point values	1.5 mg OCA Titrating to 3 mg OCA	5 mg OCA Titrating to 10 mg OCA	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	26	25	
Units: U/L				
median (inter-quartile range (Q1-Q3))	-8.0 (-20.0 to 19.0)	0.5 (-17.5 to 32.8)	-14.0 (-35.5 to 8.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Week 24 Change from Baseline in total bilirubin

End point title	Week 24 Change from Baseline in total bilirubin

End point description:

End point type	Secondary

End point timeframe:
24 weeks

End point values	1.5 mg OCA Titrating to 3 mg OCA	5 mg OCA Titrating to 10 mg OCA	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	26	25	
Units: umol/L				
median (inter-quartile range (Q1-Q3))	0.8 (-1.7 to 4.3)	1.3 (-1.3 to 6.9)	0.0 (-5.1 to 4.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Week 24 Change from Baseline in direct bilirubin

End point title	Week 24 Change from Baseline in direct bilirubin

End point description:

End point type	Secondary

End point timeframe:
24 weeks

End point values	1.5 mg OCA Titrating to 3 mg OCA	5 mg OCA Titrating to 10 mg OCA	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	26	25	
Units: umol/L				
median (inter-quartile range (Q1-Q3))	0.8 (-0.9 to 0.9)	0.9 (-0.9 to 6.4)	0.0 (-1.7 to 4.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Week 24 Change from Baseline in gamma-glutamyl transferase (GGT)

End point title	Week 24 Change from Baseline in gamma-glutamyl transferase (GGT)

End point description:

End point type	Secondary

End point timeframe:
24 weeks

End point values	1.5 mg OCA Titrating to 3 mg OCA	5 mg OCA Titrating to 10 mg OCA	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	26	25	
Units: U/L				
median (inter-quartile range (Q1-Q3))	-79.0 (-171.0 to -9.7)	-78.5 (-235.5 to 14.0)	-89.0 (-167.0 to 20.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Week 24 Change from Baseline in fibroblast growth factor - 19 (FGF-19)

End point title	Week 24 Change from Baseline in fibroblast growth factor - 19 (FGF-19)

End point description:

End point type	Secondary
End point timeframe: 24 weeks	

End point values	1.5 mg OCA Titrating to 3 mg OCA	5 mg OCA Titrating to 10 mg OCA	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	26	25	
Units: pg/mL				
median (inter-quartile range (Q1-Q3))	32.00 (-16.00 to 110.00)	147.00 (-6.35 to 714.50)	-19.50 (-79.56 to 28.00)	

Statistical analyses

No statistical analyses for this end point

Secondary: Week 24 Change from baseline in C4

End point title	Week 24 Change from baseline in C4
End point description:	

End point type	Secondary
End point timeframe: 24 weeks	

End point values	1.5 mg OCA Titrating to 3 mg OCA	5 mg OCA Titrating to 10 mg OCA	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	26	25	
Units: ng/mL				
median (inter-quartile range (Q1-Q3))	-2.80 (-7.50 to 0.55)	-2.90 (-6.94 to -1.12)	0.05 (-2.25 to 10.84)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From informed consent to end of double-blind phase study participation

Adverse event reporting additional description:

Adverse event reporting is based on safety population, where treatment group is defined by the treatment actually received. One (1) placebo subject actually received 5mg OCA titrating to 10mg OCA. All adverse event summaries are based on treatment-emergent adverse events.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	1.5 mg OCA Titrating to 3 mg OCA

Reporting group description:

Subjects randomized to 1.5 mg OCA will take 1.5 mg OCA daily for 12 weeks. If tolerated, the dose will be increased to 3 mg OCA daily for an additional 12 weeks.

Reporting group title	5 mg OCA Titrating to 10 mg OCA

Reporting group description:

Subjects randomized to 5 mg OCA will take 5 mg OCA daily for 12 weeks. If tolerated, the dose will be increased to 10 mg OCA daily for an additional 12 weeks.

Reporting group title	Placebo

Reporting group description:

Subjects randomized to placebo will take placebo daily for 24 weeks.

Serious adverse events	1.5 mg OCA Titrating to 3 mg OCA	5 mg OCA Titrating to 10 mg OCA	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 25 (16.00%)	4 / 27 (14.81%)	2 / 24 (8.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	1 / 25 (4.00%)	0 / 27 (0.00%)	0 / 24 (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
Peripheral swelling			
subjects affected / exposed	1 / 25 (4.00%)	0 / 27 (0.00%)	0 / 24 (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
Gastrointestinal disorders			

Ascites			
subjects affected / exposed	0 / 25 (0.00%)	1 / 27 (3.70%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 27 (0.00%)	0 / 24 (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
Cholangitis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 27 (3.70%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis acute			
subjects affected / exposed	0 / 25 (0.00%)	1 / 27 (3.70%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 27 (0.00%)	0 / 24 (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
Infections and infestations			

Cholangitis infective			
subjects affected / exposed	1 / 25 (4.00%)	0 / 27 (0.00%)	0 / 24 (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
Pharyngitis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 27 (3.70%)	0 / 24 (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
Pneumonia bacterial			
subjects affected / exposed	0 / 25 (0.00%)	1 / 27 (3.70%)	0 / 24 (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
Pseudomonal sepsis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 27 (0.00%)	0 / 24 (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

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

Non-serious adverse events	1.5 mg OCA Titrating to 3 mg OCA	5 mg OCA Titrating to 10 mg OCA	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 25 (92.00%)	26 / 27 (96.30%)	21 / 24 (87.50%)
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 25 (8.00%)	0 / 27 (0.00%)	2 / 24 (8.33%)
occurrences (all)	3	0	2
Blood bilirubin increased			
subjects affected / exposed	1 / 25 (4.00%)	3 / 27 (11.11%)	3 / 24 (12.50%)
occurrences (all)	1	3	3
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 25 (0.00%)	2 / 27 (7.41%)	0 / 24 (0.00%)
occurrences (all)	0	3	0
Headache			

subjects affected / exposed	2 / 25 (8.00%)	2 / 27 (7.41%)	0 / 24 (0.00%)
occurrences (all)	3	2	0
Paraesthesia			
subjects affected / exposed	0 / 25 (0.00%)	2 / 27 (7.41%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 25 (4.00%)	3 / 27 (11.11%)	2 / 24 (8.33%)
occurrences (all)	2	3	2
Oedema peripheral			
subjects affected / exposed	1 / 25 (4.00%)	2 / 27 (7.41%)	0 / 24 (0.00%)
occurrences (all)	3	2	0
Pyrexia			
subjects affected / exposed	3 / 25 (12.00%)	4 / 27 (14.81%)	1 / 24 (4.17%)
occurrences (all)	5	4	1
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 25 (0.00%)	2 / 27 (7.41%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 25 (4.00%)	0 / 27 (0.00%)	2 / 24 (8.33%)
occurrences (all)	2	0	2
Abdominal pain			
subjects affected / exposed	2 / 25 (8.00%)	2 / 27 (7.41%)	4 / 24 (16.67%)
occurrences (all)	2	3	5
Abdominal pain upper			
subjects affected / exposed	1 / 25 (4.00%)	2 / 27 (7.41%)	4 / 24 (16.67%)
occurrences (all)	2	2	4
Ascites			
subjects affected / exposed	1 / 25 (4.00%)	1 / 27 (3.70%)	2 / 24 (8.33%)
occurrences (all)	1	2	2
Constipation			
subjects affected / exposed	0 / 25 (0.00%)	2 / 27 (7.41%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Crohn's disease			

subjects affected / exposed	0 / 25 (0.00%)	2 / 27 (7.41%)	1 / 24 (4.17%)
occurrences (all)	0	2	1
Diarrhoea			
subjects affected / exposed	1 / 25 (4.00%)	3 / 27 (11.11%)	2 / 24 (8.33%)
occurrences (all)	1	3	3
Frequent bowel movements			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	3
Nausea			
subjects affected / exposed	2 / 25 (8.00%)	6 / 27 (22.22%)	3 / 24 (12.50%)
occurrences (all)	2	7	3
Vomiting			
subjects affected / exposed	1 / 25 (4.00%)	1 / 27 (3.70%)	4 / 24 (16.67%)
occurrences (all)	1	1	4
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	2 / 25 (8.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	2	0	0
Hyperbilirubinaemia			
subjects affected / exposed	1 / 25 (4.00%)	2 / 27 (7.41%)	0 / 24 (0.00%)
occurrences (all)	1	2	0
Jaundice			
subjects affected / exposed	2 / 25 (8.00%)	1 / 27 (3.70%)	1 / 24 (4.17%)
occurrences (all)	2	1	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 25 (4.00%)	1 / 27 (3.70%)	3 / 24 (12.50%)
occurrences (all)	1	1	3
Nasal congestion			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Oropharyngeal pain			
subjects affected / exposed	2 / 25 (8.00%)	3 / 27 (11.11%)	1 / 24 (4.17%)
occurrences (all)	2	3	1
Skin and subcutaneous tissue disorders			

Pruritus			
subjects affected / exposed	15 / 25 (60.00%)	18 / 27 (66.67%)	11 / 24 (45.83%)
occurrences (all)	31	38	17
Urticaria			
subjects affected / exposed	2 / 25 (8.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	2	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 25 (0.00%)	3 / 27 (11.11%)	1 / 24 (4.17%)
occurrences (all)	0	3	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 25 (8.00%)	1 / 27 (3.70%)	1 / 24 (4.17%)
occurrences (all)	5	1	1
Back pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 27 (0.00%)	3 / 24 (12.50%)
occurrences (all)	1	0	3
Sinusitis			
subjects affected / exposed	1 / 25 (4.00%)	3 / 27 (11.11%)	0 / 24 (0.00%)
occurrences (all)	1	3	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 25 (0.00%)	2 / 27 (7.41%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Urinary tract infection			
subjects affected / exposed	2 / 25 (8.00%)	1 / 27 (3.70%)	2 / 24 (8.33%)
occurrences (all)	2	1	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	3 / 24 (12.50%)
occurrences (all)	0	0	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 September 2014	Amendment 2
26 August 2015	Amendment 3
08 February 2016	Amendment 4
18 March 2016	Amendment 5

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported