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	22 March 2018

Results information

Result version number	v2 (current)
This version publication date	28 June 2021
First version publication date	23 March 2018
Version creation reason	• New data added to full data set Updating with long-term safety extension (LTSE) phase results.

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	9520 Towne Centre Drive, Suite 200, San Diego, CA, United States, 92121
Public contact	Medical Information , Intercept Pharmaceuticals, Inc., +1.844. 782.4278, medinfo@interceptpharma.com
Scientific contact	Medical Information , Intercept Pharmaceuticals, Inc., +1.844. 782.4278, medinfo@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	Final
Date of interim/final analysis	22 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 March 2017
Global end of trial reached?	Yes
Global end of trial date	22 March 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This was a phase 2, double-blind (DB), placebo-controlled trial in participants with primary sclerosing cholangitis to evaluate the effect of obeticholic acid on liver biochemistry, in particular, serum alkaline phosphatase; and, safety. The LTSE phase was conducted to evaluate the safety, tolerability, and efficacy of long-term, open-label use of obeticholic acid (OCA) in participants with primary sclerosing cholangitis who had completed the DB phase of the study.

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (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	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. All participants were required to undergo thorough screening procedures, to confirm they met the eligibility criteria, during the 30-day period preceding the first dose.

Pre-assignment

Screening details:

DB Phase: 77 participants were randomized to receive placebo, 1.5 milligrams (mg) OCA titrated to 3 mg OCA or 5 mg OCA titrated to 10 mg OCA; 1 participant did not receive treatment, 1 participant received 5 mg OCA titrated to 10 mg OCA instead of placebo. LTSE Phase: Open-label OCA doses up to 10 mg daily were evaluated.

Period 1

Period 1 title	DB Phase
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:

Participants randomized to 1.5 mg OCA took 1.5 mg OCA daily for 12 weeks during the DB phase. If tolerated, the dose was 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:

Participants randomized to 1.5 mg OCA took 1.5 mg OCA daily for 12 weeks. If tolerated, the dose was increased to 3 mg OCA daily for an additional 12 weeks.

Arm title	5 mg OCA Titrating to 10 mg OCA

Arm description:

Participants randomized to 5 mg OCA took 5 mg OCA daily for 12 weeks during the DB phase. If tolerated, the dose was 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:

Participants randomized to 5 mg OCA took 5 mg OCA daily for 12 weeks. If tolerated, the dose was increased to 10 mg OCA daily for an additional 12 weeks.

Arm title	Placebo

Arm description:

Participants randomized to placebo took placebo daily for 24 weeks during the DB phase.

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:

Participants randomized to placebo took 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
Received At Least 1 Dose Of Study Drug	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: One participant randomized to receive 1.5 mg OCA titrating to 3 mg OCA withdrew prior to dosing.

Period 2

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

Arms

Arm title	LTSE OCA Total

Arm description:

Following completion of the DB phase, participants were asked to reconfirm their consent for participation in the LTSE phase (planned as a further 24 months) beginning at 5 or 10 mg OCA, based on the last treatment received during the DB phase. Doses up to 10 mg daily were evaluated. All participants received open-label OCA during the LTSE phase of the study.

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:

All participants received open-label OCA during the LTSE phase of the study. Participants started treatment at 5 mg OCA once daily, except that those participants who completed treatment in the DB phase with 10 mg OCA once daily would continue at 10 mg OCA unless safety and tolerability warranted a dose reduction to 5 mg. Those participants who did not up-titrate their dose at DB Week 12 could remain on their DB dose at LTSE Day 1 or start at 5 mg per Investigator decision based on safety and tolerability of the DB dose at Week 24.

Number of subjects in period 2[2]	LTSE OCA Total
Started	59
Received At Least 1 Dose Of Study Drug	59
Completed	35
Not completed	24
Consent withdrawn by subject	6
Physician decision	2
Adverse event, non-fatal	10
Pruritus	4
Participant Moved	1
Lost to follow-up	1

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Eligible participants who completed the DB phase could enroll in the LTSE phase.

Baseline characteristics

Reporting groups	
Reporting group title	1.5 mg OCA Titrating to 3 mg OCA
Reporting group description:	
Participants randomized to 1.5 mg OCA took 1.5 mg OCA daily for 12 weeks during the DB phase. If tolerated, the dose was 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:	
Participants randomized to 5 mg OCA took 5 mg OCA daily for 12 weeks during the DB phase. If tolerated, the dose was increased to 10 mg OCA daily for an additional 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Participants randomized to placebo took placebo daily for 24 weeks during the DB phase.	

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: Units/Litre (U/L)			
arithmetic mean	422.5	428.5	562.8
standard deviation	± 123.07	± 178.19	± 300.22
Total Bilirubin			
Units: Micromoles (umol)/L			
arithmetic mean	16.3	19.4	20.9
standard deviation	± 8.17	± 10.94	± 11.48
Weight			
Units: Kilograms (kg)			
arithmetic mean	74.5	73.6	73.0
standard deviation	± 12.51	± 12.76	± 12.95
Height			
Units: Centimetre			
arithmetic mean	174.4	170.4	172.6
standard deviation	± 8.95	± 11.61	± 10.70
Body Mass Index			
Units: kg/metre squared			
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: Units/Litre (U/L) arithmetic mean standard deviation	 -		
Total Bilirubin Units: Micromoles (umol)/L arithmetic mean standard deviation	 -		
Weight Units: Kilograms (kg) arithmetic mean standard deviation	 -		
Height Units: Centimetre arithmetic mean standard deviation	 -		
Body Mass Index Units: kg/metre squared 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:	
Participants randomized to 1.5 mg OCA took 1.5 mg OCA daily for 12 weeks during the DB phase. If tolerated, the dose was 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:	
Participants randomized to 5 mg OCA took 5 mg OCA daily for 12 weeks during the DB phase. If tolerated, the dose was increased to 10 mg OCA daily for an additional 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Participants randomized to placebo took placebo daily for 24 weeks during the DB phase.	
Reporting group title	LTSE OCA Total
Reporting group description:	
Following completion of the DB phase, participants were asked to reconfirm their consent for participation in the LTSE phase (planned as a further 24 months) beginning at 5 or 10 mg OCA, based on the last treatment received during the DB phase. Doses up to 10 mg daily were evaluated. All participants received open-label OCA during the LTSE phase of the study.	

Primary: DB Phase: Change From Baseline In Serum ALP

End point title	DB Phase: Change From Baseline In Serum 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. Results are reported in U/L.	
End point type	Primary
End point timeframe:	
Baseline, Week 24	

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 compared the Week-24 change from Baseline in ALP between OCA treatment group and placebo using an 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

Primary: LTSE Phase: Incidence Of Adverse Events Of Special Interest (AESIs)

End point title	LTSE Phase: Incidence Of Adverse Events Of Special Interest (AESIs)[1]

End point description:

The primary safety analysis evaluated the effects of OCA treatment on AESIs of pruritus, hepatic disorders, and dyslipidemia. All adverse event (AE) summaries were restricted to treatment-emergent AEs (TEAEs), which were defined as any AEs that newly appeared, increased in frequency, or worsened in severity following initiation of investigational product. Treatment-emergent pruritus was defined as any preferred term including "Prur-". Hepatic disorder AESIs were defined using specific Hepatic Disorders Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) terms. AE lipid profile changes, defined in the Dyslipidemia SMQ, were reported. Verbatim terms were mapped to PTs and system organ classes using MedDRA version 17.1 for all AE summaries except those for hepatic disorder AESIs, which used MedDRA version 18.1. A summary of serious and all other non-serious AEs, regardless of causality, is located in the Reported Adverse Events module.

End point type	Primary

End point timeframe:

LTSE Baseline (DB Week 24) to Month 26

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analyses data were not calculated for adverse events per study protocol.

End point values	LTSE OCA Total			
Subject group type	Reporting group			
Number of subjects analysed	59			
Units: Participants				
Dyslipidaemia	1			
Hepatic Disorder	23			
Pruritus	34			

Statistical analyses

No statistical analyses for this end point

Secondary: DB Phase: Change From Baseline In Serum Alanine Transaminase (ALT)

End point title	DB Phase: Change From Baseline In Serum Alanine Transaminase (ALT)

End point description:

As a marker of hepatic biochemistry and liver function, the median change in ALT from Baseline at Week 24 is reported. Results are reported in U/L.

End point type	Secondary

End point timeframe:

Baseline, Week 24

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 5.0)	-5.5 (-30.0 to 4.5)	-19.5 (-49.0 to 4.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: DB Phase: Change From Baseline In Serum Aspartate Aminotransferase (AST)

End point title	DB Phase: Change From Baseline In Serum Aspartate Aminotransferase (AST)

End point description:

As a marker of hepatic biochemistry and liver function, the median change in AST from Baseline at Week 24 is reported. Results are reported in U/L.

End point type	Secondary

End point timeframe:

Baseline, Week 24

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: DB Phase: Change From Baseline In Serum Total Bilirubin

End point title	DB Phase: Change From Baseline In Serum Total Bilirubin

End point description:

As a marker of hepatic biochemistry and liver function, the median change in serum total bilirubin from Baseline at Week 24 is reported. Results are reported in umol/L.

End point type	Secondary

End point timeframe:

Baseline, Week 24

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: DB Phase: Change From Baseline In Serum Direct Bilirubin

End point title	DB Phase: Change From Baseline In Serum Direct Bilirubin

End point description:

As a marker of hepatic biochemistry and liver function, the median change in serum direct bilirubin from Baseline at Week 24 is reported. Results are reported in umol/L.

End point type	Secondary

End point timeframe:

Baseline, Week 24

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: DB Phase: Change From Baseline In Serum Gamma-glutamyl Transferase (GGT)

End point title	DB Phase: Change From Baseline In Serum Gamma-glutamyl Transferase (GGT)

End point description:

As a marker of hepatic biochemistry and liver function, the median change in serum GGT from Baseline at Week 24 is reported. Results are reported in U/L.

End point type	Secondary

End point timeframe:

Baseline, Week 24

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: DB Phase: Change From Baseline In Plasma Fibroblast Growth Factor-19 (FGF-19)

End point title	DB Phase: Change From Baseline In Plasma Fibroblast Growth Factor-19 (FGF-19)

End point description:

To assess farnesoid X receptor (FXR) activity, the change in FGF-19 from Baseline at Week 24 is reported. Results are reported in picograms/millilitre (pg/mL).

End point type	Secondary

End point timeframe:

Baseline, Week 24

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: DB Phase: Change From Baseline In Plasma 7α-Hydroxy-4-cholesten-3-one (C4)

End point title	DB Phase: Change From Baseline In Plasma 7α-Hydroxy-4-cholesten-3-one (C4)

End point description:

To assess FXR activity, the change in plasma C4 from Baseline at Week 24 is reported. Results are reported in nanograms (ng)/mL.

End point type	Secondary

End point timeframe:

Baseline, Week 24

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

Secondary: LTSE Phase: Change From Baseline In Serum ALP At Month 12

End point title	LTSE Phase: Change From Baseline In Serum ALP At Month 12

End point description:

The median change in serum ALP from Baseline to the last available visit is reported. The DB value at Week 24 was used as the Baseline. Results are reported in U/L.

End point type	Secondary

End point timeframe:

LTSE Baseline (DB Week 24), Month 12

End point values	LTSE OCA Total			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: U/L				
median (inter-quartile range (Q1-Q3))	-91.5 (-144.0 to -17.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: LTSE Phase: Change From Baseline In Serum ALT At Month 12

End point title	LTSE Phase: Change From Baseline In Serum ALT At Month 12

End point description:

As a marker of hepatic biochemistry and liver function, the median change in ALT from Baseline at Month 12 is reported. The DB value at Week 24 was used as the Baseline. Results are reported in U/L.

End point type	Secondary

End point timeframe:

LTSE Baseline (DB Week 24), Month 12

End point values	LTSE OCA Total			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: U/L				
median (inter-quartile range (Q1-Q3))	-37.0 (-60.5 to -7.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: LTSE Phase: Change From Baseline In Serum AST At Month 12

End point title	LTSE Phase: Change From Baseline In Serum AST At Month 12

End point description:

As a marker of hepatic biochemistry and liver function, the median change in AST from Baseline at Month 12 is reported. The DB value at Week 24 was used as the Baseline. Results are reported in U/L.

End point type	Secondary

End point timeframe:

LTSE Baseline (DB Week 24), Month 12

End point values	LTSE OCA Total			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: U/L				
median (inter-quartile range (Q1-Q3))	-14.5 (-30.5 to 9.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: LTSE Phase: Change From Baseline In Serum Total Bilirubin At Month 12

End point title	LTSE Phase: Change From Baseline In Serum Total Bilirubin At Month 12

End point description:

As a marker of hepatic biochemistry and liver function, the median change in serum total bilirubin from Baseline at Month 12 is reported. The DB value at Week 24 was used as the Baseline. Results are reported in umol/L.

End point type	Secondary

End point timeframe:

LTSE Baseline (DB Week 24), Month 12

End point values	LTSE OCA Total			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: umol/L				
median (inter-quartile range (Q1-Q3))	0.5 (-1.7 to 5.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: LTSE Phase: Change From Baseline In Serum Direct Bilirubin At Month 12

End point title	LTSE Phase: Change From Baseline In Serum Direct Bilirubin At Month 12

End point description:

As a marker of hepatic biochemistry and liver function, the median change in serum direct bilirubin from Baseline at Month 12 is reported. The DB value at Week 24 was used as the Baseline. Results are reported in umol/L.

End point type	Secondary

End point timeframe:

LTSE Baseline (DB Week 24), Month 12

End point values	LTSE OCA Total			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: umol/L				
median (inter-quartile range (Q1-Q3))	0.0 (-1.7 to 1.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: LTSE Phase: Change From Baseline In Serum GGT At Month 12

End point title	LTSE Phase: Change From Baseline In Serum GGT At Month 12

End point description:

As a marker of hepatic biochemistry and liver function, the median change in serum GGT from Baseline at Month 12 is reported. The DB value at Week 24 was used as the Baseline. Results are reported in U/L.

End point type	Secondary

End point timeframe:

LTSE Baseline (DB Week 24), Month 12

End point values	LTSE OCA Total			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: U/L				
median (inter-quartile range (Q1-Q3))	-120.3 (-238.0 to 39.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: LTSE Phase: Change From Baseline In Albumin At Month 12

End point title	LTSE Phase: Change From Baseline In Albumin At Month 12

End point description:

As a marker of hepatic biochemistry and liver function, the median change in albumin from Baseline at Month 12 is reported. The DB value at Week 24 was used as the Baseline. Results are reported in grams (g)/L.

End point type	Secondary

End point timeframe:

LTSE Baseline (DB Week 24), Month 12

End point values	LTSE OCA Total			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: g/L				
median (inter-quartile range (Q1-Q3))	-0.5 (-3.5 to 1.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: LTSE Phase: Change From Baseline In INR At Month 12

End point title	LTSE Phase: Change From Baseline In INR At Month 12

End point description:

As a marker of hepatic biochemistry and liver function, the median change in INR from Baseline at Month 12 is reported. The DB value at Week 24 was used as the Baseline.

End point type	Secondary

End point timeframe:

LTSE Baseline (DB Week 24), Month 12

End point values	LTSE OCA Total			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Ratio				
median (inter-quartile range (Q1-Q3))	0.0 (0.0 to 0.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: LTSE Phase: Change From Baseline In Transient Elastography (TE) At Month 12

End point title	LTSE Phase: Change From Baseline In Transient Elastography (TE) At Month 12

End point description:

As a marker of hepatic inflammation and fibrosis, the median change in TE, as a measure of hepatic stiffness, from Baseline at Month 12 is reported. The DB value at Week 24 was used as the Baseline. Results are reported in kilopascal (kPa).

End point type	Secondary

End point timeframe:

LTSE Baseline (DB Week 24), Month 12

End point values	LTSE OCA Total			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: kPa				
median (inter-quartile range (Q1-Q3))	1.8 (-0.8 to 6.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: LTSE Phase: Change From Baseline In Enhanced Liver Fibrosis (ELF) At Month 12

End point title	LTSE Phase: Change From Baseline In Enhanced Liver Fibrosis (ELF) At Month 12

End point description:

As a marker of hepatic inflammation and fibrosis, the change in ELF score from Baseline at Month 12 is reported. The ELF score and its components (hyaluronic acid [HA]; procollagen-3 N-terminal peptide [P3NP]; tissue inhibitor of metalloproteinase 1 [TIMP-1]) was calculated as follows: 2.278 + 0.851 x ln(HA (ng/mL)) + 0.751 x ln(P3NP (ng/mL)) + 0.394 x ln(TIMP-1 (ng/mL). The DB value at Week 24 was used as the Baseline. An increase in score indicates an improvement/worsening of symptoms.

End point type	Secondary

End point timeframe:

LTSE Baseline (DB Week 24), Month 12

End point values	LTSE OCA Total			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Units on a scale				
median (inter-quartile range (Q1-Q3))	0.3 (0.0 to 1.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: LTSE Phase: Change From Baseline In Plasma FGF-19 At Month 12

End point title	LTSE Phase: Change From Baseline In Plasma FGF-19 At Month 12

End point description:

To assess FXR activity, the change in FGF-19 from Baseline at Month 12 is reported. The DB value at

Week 24 was used as the Baseline. Results are reported in pg/mL.

End point type	Secondary

End point timeframe:

LTSE Baseline (DB Week 24), Month 12

End point values	LTSE OCA Total			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: pg/mL				
median (inter-quartile range (Q1-Q3))	77.7 (-37.0 to 194.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: LTSE Phase: Change From Baseline In Plasma C4 At Month 12

End point title	LTSE Phase: Change From Baseline In Plasma C4 At Month 12

End point description:

To assess FXR activity, the change in plasma C4 from Baseline at Month 12 is reported. The DB value at Week 24 was used as the Baseline. Results are reported in ng/mL.

End point type	Secondary

End point timeframe:

LTSE Baseline (DB Week 24), Month 12

End point values	LTSE OCA Total			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: ng/mL				
median (inter-quartile range (Q1-Q3))	-3.8 (-8.1 to -0.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: LTSE Phase: Participants Experiencing Ulcerative Colitis Remission At Month 12

End point title	LTSE Phase: Participants Experiencing Ulcerative Colitis Remission At Month 12

End point description:

To assess inflammatory bowel disease (IBD) activity, the number of participants experiencing ulcerative

colitis remission at Month 12 is reported. Remission was defined as a partial Mayo score of ≤2 with no individual sub-score exceeding 1 point.

End point type	Secondary

End point timeframe:

Month 12

End point values	LTSE OCA Total			
Subject group type	Reporting group			
Number of subjects analysed	59			
Units: Participants				
Yes	16			
No	0			

Statistical analyses

No statistical analyses for this end point

Secondary: LTSE Phase: Participants Experiencing Crohn’s Disease Remission At Month 12

End point title	LTSE Phase: Participants Experiencing Crohn’s Disease Remission At Month 12

End point description:

To assess IBD activity, the number of participants experiencing Crohn’s Disease remission at Month 12 is reported. Remission was defined as a Crohn’s Disease Activity Index (CDAI) score of <150.

End point type	Secondary

End point timeframe:

Month 12

End point values	LTSE OCA Total			
Subject group type	Reporting group			
Number of subjects analysed	59			
Units: Participants				
Yes	5			
No	1			

Statistical analyses

No statistical analyses for this end point

Secondary: LTSE Phase: Change From Baseline In Total Bile Acids At Month 12

End point title	LTSE Phase: Change From Baseline In Total Bile Acids At Month 12

End point description:

To assess the effects on bile acids, the median change in total bile acids from Baseline at Month 12 is reported. The DB value at Week 24 was used as the Baseline. Results are reported in umol/L.

End point type	Secondary

End point timeframe:

Month 12

End point values	LTSE OCA Total			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: umol/L				
median (inter-quartile range (Q1-Q3))	-1.59 (-8.12 to 6.49)			

Statistical analyses

No statistical analyses for this end point

Secondary: LTSE Phase: Change From Baseline In Pruritus Visual Analogue Scale (VAS) At Month 12

End point title	LTSE Phase: Change From Baseline In Pruritus Visual Analogue Scale (VAS) At Month 12

End point description:

To assess the effects on disease-specific symptoms, the median change in the pruritus VAS score from Baseline at Month 12 is reported. The score is derived from the VAS participant questionnaire, which has the participant draw a line anywhere on a scale that best represents the severity of the itch; the scale ranges from 0 (no itching) to 10 (worst possible itching), in increments of 2. An increase in score represents an increase in severity of symptoms. The DB value at Week 24 was used as the Baseline.

End point type	Secondary

End point timeframe:

LTSE Baseline (DB Week 24), Month 12

End point values	LTSE OCA Total			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Units on a scale				
median (inter-quartile range (Q1-Q3))	1.0 (0.0 to 20.0)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

DB Phase: From informed consent to end of DB phase study participation, up to 24 weeks. LTSE Phase: Baseline (DB Week 24) to Month 26.

Adverse event reporting additional description:

Adverse event reporting is based on safety population, where treatment group was defined by the treatment actually received. One (1) placebo participant actually received 5 mg OCA titrating to 10 mg OCA. All adverse event summaries are based on TEAEs. Verbatim terms were mapped using MedDRA 17.1; MedDRA 18.1 was used for hepatic disorder AESIs.

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:

Participants randomized to 1.5 mg OCA will take 1.5 mg OCA daily for 12 weeks during the DB phase. 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:

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

Reporting group title	Placebo

Reporting group description:

Participants randomized to placebo will take placebo daily for 24 weeks during the DB phase.

Reporting group title	LTSE OCA Total

Reporting group description:

Following completion of the DB phase, participants were asked to reconfirm their consent for participation in the LTSE phase (planned as a further 24 months) beginning at 5 or 10 mg OCA, based on the last treatment received during the DB phase. Doses up to 10 mg daily were evaluated. All participants received open-label OCA during the LTSE phase of the study.

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			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (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
Injury, poisoning and procedural			

complications			
Anastomotic leak			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (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
Ankle fracture			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (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
Delayed recovery from anaesthesia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (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
Forearm fracture			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (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			
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
Abdominal pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (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
Abdominal pain upper			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (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
Colon dysplasia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (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
Crohn's disease			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (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
Gastric ulcer			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (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 haemorrhage			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (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
Pouchitis			

subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (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
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
Bile duct obstruction			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (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
Respiratory, thoracic and mediastinal disorders			

Pulmonary oedema			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (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			
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
Peritonitis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (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
Abdominal abscess			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (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
Enteritis infectious			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (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 viral			

subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (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
Pelvic abscess			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (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
Perirectal abscess			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (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
Pneumonia pneumococcal			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (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

Serious adverse events	LTSE OCA Total		
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 59 (32.20%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Anastomotic leak			

subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ankle fracture				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Delayed recovery from anaesthesia				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Forearm fracture				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Oedema peripheral				
subjects affected / exposed	0 / 59 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peripheral swelling				
subjects affected / exposed	0 / 59 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Ascites				
subjects affected / exposed	0 / 59 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophageal varices haemorrhage				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Pancreatitis				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	2 / 59 (3.39%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colon dysplasia				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Crohn's disease				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pouchitis				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				

subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholangitis			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholangitis acute			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis acute			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperbilirubinaemia			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bile duct obstruction			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary oedema			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
Cholangitis infective			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pharyngitis			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia bacterial			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pseudomonal sepsis			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peritonitis			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Abdominal abscess			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enteritis infectious			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis viral			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pelvic abscess			

subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Perirectal abscess			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia pneumococcal			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 4.99 %

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
Alanine aminotransferase increased			
subjects affected / exposed	1 / 25 (4.00%)	0 / 27 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	1
Liver function test abnormal			

subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
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%)	1 / 24 (4.17%)
occurrences (all)	1	2	1
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
Colitis ulcerative			
subjects affected / exposed	1 / 25 (4.00%)	0 / 27 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	1
Haemorrhoids			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Abdominal pain lower			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Varices oesophageal			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Bile duct stenosis			

subjects affected / exposed	1 / 25 (4.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 25 (0.00%)	2 / 27 (7.41%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Jaundice			
subjects affected / exposed	2 / 25 (8.00%)	1 / 27 (3.70%)	1 / 24 (4.17%)
occurrences (all)	2	1	1
Cholangitis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 27 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	3
Portal hypertension			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
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
Rash			
subjects affected / exposed	1 / 25 (4.00%)	1 / 27 (3.70%)	1 / 24 (4.17%)
occurrences (all)	1	1	2
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
Bronchitis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
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
Hypokalaemia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	2	0	0

Non-serious adverse events	LTSE OCA Total		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	53 / 59 (89.83%)		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences (all)	2		
Blood bilirubin increased			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	4		
Alanine aminotransferase increased			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Liver function test abnormal			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences (all)	2		
Paraesthesia			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	5		
Oedema peripheral			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	4		
Pyrexia			

subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	6		
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Abdominal pain			
subjects affected / exposed	7 / 59 (11.86%)		
occurrences (all)	8		
Abdominal pain upper			
subjects affected / exposed	7 / 59 (11.86%)		
occurrences (all)	8		
Ascites			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	4		
Constipation			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	4		
Crohn's disease			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	8 / 59 (13.56%)		
occurrences (all)	13		
Frequent bowel movements			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	8 / 59 (13.56%)		
occurrences (all)	10		
Vomiting			

subjects affected / exposed	8 / 59 (13.56%)		
occurrences (all)	8		
Colitis ulcerative			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	6		
Haemorrhoids			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	6		
Abdominal pain lower			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Varices oesophageal			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Hyperbilirubinaemia			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Jaundice			
subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	5		
Cholangitis			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	6		
Portal hypertension			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	2		
Nasal congestion			

subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	33 / 59 (55.93%)		
occurrences (all)	62		
Urticaria			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	4		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	4		
Sinusitis			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences (all)	3		
Upper respiratory tract infection			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences (all)	2		

Urinary tract infection subjects affected / exposed occurrences (all)	4 / 59 (6.78%) 4		
Bronchitis subjects affected / exposed occurrences (all)	4 / 59 (6.78%) 4		
Influenza subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 4		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	2 / 59 (3.39%) 2		
Hypokalaemia subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 September 2014	Amendment 2: - Changed maximum frequency of dose titrations during the LTSE phase from monthly to every 3 months. - Added 2 additional evaluations for disease-specific symptoms: Pruritus 5-D questionnaire and CDAI. - Changed the co-primary efficacy endpoints of Week 12 and Week 24 change from Baseline in ALP to a single primary endpoint of Week 24 change from Baseline in ALP. - Revised secondary efficacy analyses to employ a hierarchical approach. - Added a formal unblinded interim analysis for planning purposes. - Required that, at a minimum, the occurrence of 2 life-threatening serious AEs (SAEs) or an SAE resulting in death would trigger an unscheduled and unblinded review of the data by the data safety monitoring committee to determine if the trial should continue. - Added criterion requiring study withdrawal of participants who experience 3 or more IBD flares in 1 year. - Specified categories of hospitalizations that are not to be considered SAEs.
26 August 2015	Amendment 3: - Included changes to clarify eligibility criteria and procedures. - Added intolerable pruritus as a criterion for discontinuation from the trial. - Added statins as an allowed medication. - Clarified that participants would not automatically enroll into the LTSE phase and be required to reconfirm their consent, but instead would be asked to reconfirm their consent to participate in the LTSE phase. - Clarified that if the Investigator did not want a participant's dose to be titrated in line with the protocol recommendations, the Investigator may (not should) discuss this decision with the Medical Monitor. - Added a safety contact at Week 2 of the LTSE phase. - Deleted: A few Sponsor representatives may be unblinded during the trial/DB phase of the study. If there are any findings regarding safety, tolerability, or efficacy that indicate an alternative optimal LTSE starting dose, the starting dose in the LTSE may be reduced. - Clarified that the doses of OCA in the LTSE phase should be titrated, rather than may be titrated.
08 February 2016	Amendment 4: - Clarified eligibility criteria.
18 March 2016	Amendment 5: - Clarified that intermediate doses (for example, 6.5 mg) may be considered as deemed appropriate by the Investigator during the LTSE phase, and that the dose should not exceed 10 mg. - Clarified criteria, investigational product storage instructions. - Clarified titration adjustments.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to administrative reasons, the study was terminated by the Sponsor prior to most participants completing LTSE Month 24.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32165251