Clinical trial results:
A Phase 2, Randomized, Double-Blind, Placebo Controlled Study Evaluating the Safety, Tolerability, and Efficacy of GS-9674 in Subjects with Primary Sclerosing Cholangitis Without Cirrhosis

Summary

EudraCT number	2016-002442-23
Trial protocol	GB AT
Global end of trial date	

Results information

Result version number	v1
This version publication date	31 July 2019
First version publication date	31 July 2019

Trial information

Trial identification

Sponsor protocol code	GS-US-428-4025

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02943460
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, CA, United States, 94404
Public contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com
Scientific contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.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	26 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 February 2018
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the safety and tolerability of cilofexor in adults with primary sclerosing cholangitis (PSC).

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 November 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	United States: 36
Country: Number of subjects enrolled	Canada: 8
Worldwide total number of subjects	52
EEA total number of subjects	8

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)	52
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in North America and Europe. The first participant was screened on 29 November 2016. The last visit in blinded study phase occurred on 28 February 2018.

Pre-assignment

Screening details:

105 participants were screened.

Period 1

Period 1 title	Blinded Study Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Cilofexor 100 mg

Arm description:

Cilofexor 100 mg tablet + placebo to match cilofexor 30 mg tablet once daily for 12 weeks

Arm type	Experimental
Investigational medicinal product name	Cilofexor
Investigational medicinal product code	
Other name	GS-9674
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

100 mg administered once daily

Investigational medicinal product name	Placebo to match cilofexor 30 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered once daily

Arm title	Cilofexor 30 mg

Arm description:

Cilofexor 30 mg tablet + placebo to match cilofexor 100 mg tablet once daily for 12 weeks

Arm type	Experimental
Investigational medicinal product name	Cilofexor
Investigational medicinal product code	
Other name	GS-9674
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

30 mg administered once daily

Investigational medicinal product name	Placebo to match cilofexor 100 mg
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered once daily

Arm title	Placebo

Arm description:

Placebo to match cilofexor 30 mg tablet + placebo to match cilofexor 100 mg tablet once daily for 12 weeks

Arm type	Placebo
Investigational medicinal product name	Placebo to match cilofexor 30 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered once daily

Investigational medicinal product name	Placebo to match cilofexor 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered once daily

Number of subjects in period 1	Cilofexor 100 mg	Cilofexor 30 mg	Placebo
Started	22	20	10
Completed	19	19	10
Not completed	3	1	0
Withdrew Consent	-	1	-
Adverse Event	3	-	-

Period 2

Period 2 title	Open Label Extension (OLE) Phase
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes

Arm title	Cilofexor 100 mg to Cilofexor 100 mg
Arm description: Cilofexor 100 mg tablet once daily for an additional 96 weeks	
Arm type	Experimental
Investigational medicinal product name	Cilofexor
Investigational medicinal product code	
Other name	GS-9674
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 100 mg administered once daily	
Arm title	Cilofexor 30 mg to Cilofexor 100 mg
Arm description: Cilofexor 100 mg tablet once daily for an additional 96 weeks	
Arm type	Experimental
Investigational medicinal product name	Cilofexor
Investigational medicinal product code	
Other name	GS-9674
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 100 mg administered once daily	
Arm title	Placebo to Cilofexor 100 mg
Arm description: Cilofexor 100 mg tablet once daily for an additional 96 weeks	
Arm type	Experimental
Investigational medicinal product name	Cilofexor
Investigational medicinal product code	
Other name	GS-9674
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 100 mg administered once daily	

Number of subjects in period 2[1]	Cilofexor 100 mg to Cilofexor 100 mg	Cilofexor 30 mg to Cilofexor 100 mg	Placebo to Cilofexor 100 mg
Started	19	18	9
Completed	0	0	0
Not completed	19	18	9
Withdrew Consent	1	1	-
Adverse Event	-	2	1
Still in Open Label Extension Phase	18	14	8
Investigator's Discretion	-	1	-

Notes:

[1] - 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: 1 participant in the Placebo group discontinued study drug in the Blinded Phase, but did not discontinue the study. 1 participant from the Cilofexor 30 mg group completed the Blinded Study Phase, but did not continue in the OLE Phase. 1 participant from the Placebo group who discontinued study drug in the Blinded Phase did not enter the OLE Phase.

Baseline characteristics

Reporting groups	
Reporting group title	Cilofexor 100 mg
Reporting group description:	
Cilofexor 100 mg tablet + placebo to match cilofexor 30 mg tablet once daily for 12 weeks	
Reporting group title	Cilofexor 30 mg
Reporting group description:	
Cilofexor 30 mg tablet + placebo to match cilofexor 100 mg tablet once daily for 12 weeks	
Reporting group title	Placebo
Reporting group description:	
Placebo to match cilofexor 30 mg tablet + placebo to match cilofexor 100 mg tablet once daily for 12 weeks	

Reporting group values	Cilofexor 100 mg	Cilofexor 30 mg	Placebo
Number of subjects	22	20	10
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	42	46	42
standard deviation	± 8.6	± 12.1	± 10.9
Gender categorical Units: Subjects			
Female	11	6	5
Male	11	14	5
Ethnicity Units: Subjects			
Hispanic or Latino	0	3	0
Not Hispanic or Latino	21	17	9
Unknown or Not Reported	1	0	1
Race Units: Subjects			
Asian	0	2	1
Black or African American	4	3	1
White	17	15	7
Not Permitted	0	0	1
Other	1	0	0

Reporting group values	Total		
Number of subjects	52		
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean			
standard deviation	-		

Gender categorical Units: Subjects			
Female	22		
Male	30		
Ethnicity Units: Subjects			
Hispanic or Latino	3		
Not Hispanic or Latino	47		
Unknown or Not Reported	2		
Race Units: Subjects			
Asian	3		
Black or African American	8		
White	39		
Not Permitted	1		
Other	1		

End points

End points reporting groups

Reporting group title	Cilofexor 100 mg
Reporting group description:	
Cilofexor 100 mg tablet + placebo to match cilofexor 30 mg tablet once daily for 12 weeks	
Reporting group title	Cilofexor 30 mg
Reporting group description:	
Cilofexor 30 mg tablet + placebo to match cilofexor 100 mg tablet once daily for 12 weeks	
Reporting group title	Placebo
Reporting group description:	
Placebo to match cilofexor 30 mg tablet + placebo to match cilofexor 100 mg tablet once daily for 12 weeks	
Reporting group title	Cilofexor 100 mg to Cilofexor 100 mg
Reporting group description:	
Cilofexor 100 mg tablet once daily for an additional 96 weeks	
Reporting group title	Cilofexor 30 mg to Cilofexor 100 mg
Reporting group description:	
Cilofexor 100 mg tablet once daily for an additional 96 weeks	
Reporting group title	Placebo to Cilofexor 100 mg
Reporting group description:	
Cilofexor 100 mg tablet once daily for an additional 96 weeks	

Primary: Percentage of Participants Experiencing Treatment-Emergent Adverse Events During the Blinded Phase

End point title	Percentage of Participants Experiencing Treatment-Emergent Adverse Events During the Blinded Phase[1]

End point description:

Treatment-emergent adverse events occurring during the Blinded Phase were defined as 1 or both of the following: 1) Any adverse events (AEs) with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug in the Blinded Phase (and before the first dosing date in the Open Label Extension (OLE) Phase), or 2) Any AEs leading to premature discontinuation of study drug in the Blinded Phase. Safety Analysis Set included all participants who took at least 1 dose of study drug.

End point type	Primary

End point timeframe:

Up to 12 weeks plus 30 days

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: No statistical comparison was planned or performed.

End point values	Cilofexor 100 mg	Cilofexor 30 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	20	10	
Units: percentage of participants				
number (not applicable)	81.8	65.0	100.0	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Experiencing Treatment-Emergent Serious Adverse Events During the Blinded Phase

End point title	Percentage of Participants Experiencing Treatment-Emergent Serious Adverse Events During the Blinded Phase[2]

End point description:

A serious adverse event was defined as an event that, at any dose, resulted in any of the following: death, life-threatening, in-patient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, a congenital anomaly/birth defect, or a medically important event or reaction. Participants in the Safety Analysis Set were analyzed.

End point type	Primary

End point timeframe:

Up to 12 weeks plus 30 days

Notes:

[2] - 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: No statistical comparison was planned or performed.

End point values	Cilofexor 100 mg	Cilofexor 30 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	20	10	
Units: percentage of participants				
number (not applicable)	13.6	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Experiencing Treatment-Emergent Laboratory Abnormalities During the Blinded Phase

End point title	Percentage of Participants Experiencing Treatment-Emergent Laboratory Abnormalities During the Blinded Phase[3]

End point description:

Treatment-emergent laboratory abnormalities occurring during the Blinded Phase were defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to and including the date of last dose of study drug in the Blinded Phase plus 30 days. The Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 was used for assigning toxicity grades (0 to 4, with higher grades indicating more severity). Participants in the Safety Analysis Set were analyzed.

End point type	Primary

End point timeframe:

Up to 12 weeks plus 30 days

Notes:

[3] - 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: No statistical comparison was planned or performed.

End point values	Cilofexor 100 mg	Cilofexor 30 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	20	10	
Units: percentage of participants				
number (not applicable)				
Any Grade 1 or Higher	90.9	85.0	100.0	
Grade 1	22.7	25.0	10.0	
Grade 2	36.4	35.0	60.0	
Grade 3	27.3	20.0	30.0	
Grade 4	4.5	5.0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to the Week 12 Data Cut	
Adverse event reporting additional description:	
Safety Analysis Set included all participants who took at least 1 dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups	
Reporting group title	Cilofexor 100 mg (Blinded Phase)
Reporting group description:	
Cilofexor 100 mg tablet + placebo to match cilofexor 30 mg tablet once daily for 12 weeks	
Reporting group title	Cilofexor 30 mg (Blinded Phase)
Reporting group description:	
Cilofexor 30 mg tablet + placebo to match cilofexor 100 mg tablet once daily for 12 weeks	
Reporting group title	Placebo (Blinded Phase)
Reporting group description:	
Placebo to match cilofexor 30 mg tablet + placebo to match cilofexor 100 mg tablet once daily for 12 weeks	
Reporting group title	Cilofexor 100 mg (Open Label Phase)
Reporting group description:	
Cilofexor 100 mg tablet once daily for an additional 96 weeks	

Serious adverse events	Cilofexor 100 mg (Blinded Phase)	Cilofexor 30 mg (Blinded Phase)	Placebo (Blinded Phase)
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 22 (13.64%)	0 / 20 (0.00%)	0 / 10 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Rib fracture			
subjects affected / exposed	1 / 22 (4.55%)	0 / 20 (0.00%)	0 / 10 (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
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	0 / 10 (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
Diarrhoea			
subjects affected / exposed	1 / 22 (4.55%)	0 / 20 (0.00%)	0 / 10 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 22 (4.55%)	0 / 20 (0.00%)	0 / 10 (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			
Sepsis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	0 / 10 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 22 (4.55%)	0 / 20 (0.00%)	0 / 10 (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

Serious adverse events	Cilofexor 100 mg (Open Label Phase)		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 46 (4.35%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Rib fracture			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration			

site conditions			
Chest pain			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Cilofexor 100 mg (Blinded Phase)	Cilofexor 30 mg (Blinded Phase)	Placebo (Blinded Phase)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 22 (81.82%)	13 / 20 (65.00%)	10 / 10 (100.00%)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign neoplasm of skin			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Haemangioma			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Melanocytic naevus			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Seborrhoeic keratosis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 22 (13.64%)	2 / 20 (10.00%)	2 / 10 (20.00%)
occurrences (all)	3	2	2
Pyrexia			
subjects affected / exposed	1 / 22 (4.55%)	2 / 20 (10.00%)	0 / 10 (0.00%)
occurrences (all)	1	2	0
Chills			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Pain			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Investigations			

Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 22 (9.09%)	0 / 20 (0.00%)	1 / 10 (10.00%)
occurrences (all)	2	0	1
Alanine aminotransferase increased			
subjects affected / exposed	1 / 22 (4.55%)	0 / 20 (0.00%)	2 / 10 (20.00%)
occurrences (all)	1	0	2
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Blood bilirubin increased			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Electrocardiogram abnormal			
subjects affected / exposed	2 / 22 (9.09%)	0 / 20 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 22 (4.55%)	1 / 20 (5.00%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Hepatic enzyme increased			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Stoma site pain			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 22 (4.55%)	4 / 20 (20.00%)	2 / 10 (20.00%)
occurrences (all)	1	6	3
Dizziness			
subjects affected / exposed	2 / 22 (9.09%)	1 / 20 (5.00%)	0 / 10 (0.00%)
occurrences (all)	3	1	0
Paraesthesia			
subjects affected / exposed	1 / 22 (4.55%)	1 / 20 (5.00%)	0 / 10 (0.00%)
occurrences (all)	1	1	0

Eye disorders			
Blepharitis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	3 / 22 (13.64%)	2 / 20 (10.00%)	1 / 10 (10.00%)
occurrences (all)	3	2	1
Nausea			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	3 / 10 (30.00%)
occurrences (all)	0	1	4
Abdominal pain			
subjects affected / exposed	1 / 22 (4.55%)	0 / 20 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Diarrhoea			
subjects affected / exposed	1 / 22 (4.55%)	1 / 20 (5.00%)	0 / 10 (0.00%)
occurrences (all)	2	1	0
Abdominal distension			
subjects affected / exposed	2 / 22 (9.09%)	0 / 20 (0.00%)	1 / 10 (10.00%)
occurrences (all)	2	0	1
Abdominal discomfort			
subjects affected / exposed	1 / 22 (4.55%)	0 / 20 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	2
Vomiting			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Constipation			
subjects affected / exposed	2 / 22 (9.09%)	0 / 20 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Flatulence			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Dyspepsia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Faeces pale			

subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Noninfective sialoadenitis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Pouchitis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Tongue disorder			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Hepatitis acute			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Hepatitis cholestatic			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	7 / 22 (31.82%)	5 / 20 (25.00%)	6 / 10 (60.00%)
occurrences (all)	7	5	6
Rash			
subjects affected / exposed	1 / 22 (4.55%)	0 / 20 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Dermatitis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Urticaria			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Dermal cyst			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Rash pruritic			

subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 22 (4.55%)	2 / 20 (10.00%)	0 / 10 (0.00%)
occurrences (all)	2	2	0
Muscle spasms			
subjects affected / exposed	1 / 22 (4.55%)	2 / 20 (10.00%)	0 / 10 (0.00%)
occurrences (all)	1	2	0
Arthralgia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Flank pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Pain in extremity			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 22 (22.73%)	5 / 20 (25.00%)	2 / 10 (20.00%)
occurrences (all)	5	5	2
Upper respiratory tract infection			
subjects affected / exposed	2 / 22 (9.09%)	0 / 20 (0.00%)	1 / 10 (10.00%)
occurrences (all)	2	0	1
Viral infection			
subjects affected / exposed	2 / 22 (9.09%)	0 / 20 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Conjunctivitis			
subjects affected / exposed	1 / 22 (4.55%)	1 / 20 (5.00%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Sinusitis			

subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Respiratory tract infection			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1

Non-serious adverse events	Cilofexor 100 mg (Open Label Phase)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 46 (60.87%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign neoplasm of skin			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Haemangioma			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Melanocytic naevus			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Seborrhoeic keratosis			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	3		
Pyrexia			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	3		

Chills			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Alanine aminotransferase increased			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Blood bilirubin increased			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	2		
Electrocardiogram abnormal			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Hepatic enzyme increased			

subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Stoma site pain			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	3		
Dizziness			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Eye disorders			
Blepharitis			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	3		
Nausea			
subjects affected / exposed	4 / 46 (8.70%)		
occurrences (all)	4		
Abdominal pain			
subjects affected / exposed	4 / 46 (8.70%)		
occurrences (all)	5		
Diarrhoea			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	3		
Abdominal distension			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		

Abdominal discomfort subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 2		
Vomiting subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1		
Constipation subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Flatulence subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1		
Dyspepsia subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Faeces pale subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Noninfective sialoadenitis subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Pouchitis subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Tongue disorder subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Hepatobiliary disorders Hepatitis acute subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Hepatitis cholestatic subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Skin and subcutaneous tissue disorders			

Pruritus			
subjects affected / exposed	12 / 46 (26.09%)		
occurrences (all)	14		
Rash			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	2		
Dermatitis			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Dermal cyst			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Rash pruritic			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	2		
Muscle spasms			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Arthralgia			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Flank pain			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Pain in extremity			

subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 46 (15.22%)		
occurrences (all)	7		
Upper respiratory tract infection			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Viral infection			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Conjunctivitis			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Respiratory tract infection			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 September 2016	• Increased number of months of prior ursodeoxycholic acid (UDCA) use to allow longer duration for UDCA induced reductions in alkaline phosphatase to appear. • Added clarity that participants with nonalcoholic steatohepatitis (NASH) should be excluded and definition of inflammatory bowel disease (IBD) and liver fibrosis scoring updated. • Additional visits added for safety monitoring in the Open Label Extension. • Updated with additional available safety and PK data. • Inclusion criteria updated to further ensure participants with more advanced liver disease/cirrhosis and IBD are not included. • Prohibited concomitant mediations updated based on additional available drug-drug interaction (DDI) data. • Updated to add exclusion of chronic antibiotic use for the treatment of PSC. • Clarified that rescreening once is allowed. • Updated contraception requirements section based on DDI and pre-clinical embryofetal toxicity data now available.
21 December 2016	• Language added for clarification that direct bilirubin will be used instead of total bilirubin in FibroSURE/FibroTest® calculations in participants with Gilbert's syndrome or hemolysis, and that in subjects with FibroSURE/FibroTest® ≥0.75 may be included if a biopsy within 12 months of screening has excluded cirrhosis. • Updated to reflect final non-clinical toxicology data to support dosing beyond 12 weeks. • Updated inclusion criteria from creatinine clearance to serum creatinine. • Language added to clarify that study drug should not be dosed within 4 hours of dosing with bile acid sequestrants. • Language added to clarify retesting/rescreening eligibility for subjects. • Clarified that cirrhosis assessments include review of historical information including liver histology and FibroScan results if available. • Language added for pregnancy requirement for clarification.
09 February 2017	• Updated section on toxicity management observation for drug induced liver injury (DILI) for clarification and removed elevated serum alkaline phosphatase (ALP) as one of the close observation criteria.

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.

An unplanned review of unblinded clinical trial data was performed in this study that was not prospectively specified in the protocol. There was no impact on the overall integrity or conclusions of the study.

Notes: