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 Biliary Cholangitis Without Cirrhosis

Summary

EudraCT number	2016-002443-42
Trial protocol	GB AT
Global end of trial date	04 September 2019

Results information

Result version number	v1 (current)
This version publication date	19 September 2020
First version publication date	19 September 2020

Trial information

Trial identification

Sponsor protocol code	GS-US-427-4024

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02943447
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	Final
Date of interim/final analysis	04 September 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 September 2019
Global end of trial reached?	Yes
Global end of trial date	04 September 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the safety and tolerability of cilofexor in adults with primary biliary cholangitis
(PBC).

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	01 December 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 States: 35
Country: Number of subjects enrolled	Canada: 21
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Austria: 7
Worldwide total number of subjects	71
EEA total number of subjects	15

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)	63
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in United States, Canada, United Kingdom, and Austria. The first participant was screened on 01 December 2016. The last study visit occurred on 4 September 2019.

Pre-assignment

Screening details:

130 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	Blinded Study Phase: Cilofexor 100 mg

Arm description:

Cilofexor 100 mg tablet + placebo to match cilofexor 30 mg tablet orally 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 tablet administered orally once daily, with food

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:

Tablet(s) administered orally once daily, with food

Arm title	Blinded Study Phase: Cilofexor 30 mg

Arm description:

Cilofexor 30 mg tablet + placebo to match cilofexor 100 mg tablet orally 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 tablet administered orally once daily, with food

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:

Tablet(s) administered orally once daily, with food

Arm title	Blinded Study Phase: Placebo

Arm description:

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

Arm type	Placebo
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:

Tablet(s) administered orally once daily, with food

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:

Tablet(s) administered orally once daily, with food

Number of subjects in period 1	Blinded Study Phase: Cilofexor 100 mg	Blinded Study Phase: Cilofexor 30 mg	Blinded Study Phase: Placebo
Started	28	30	13
Completed	23	28	12
Not completed	5	2	1
Adverse event	3	-	-
Investigator`s discretion	1	-	-
Withdrew consent	1	2	1

Period 2

Period 2 title	Open-Label Extension Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes

Arm title	OLE Phase: From Cilofexor 100 mg

Arm description:

Following Blinded Study Phase, participants in the Cilofexor 100 mg group, willing to enter Open-Label Extension (OLE) Phase received open-label cilofexor 100 mg tablet orally once daily for 97.4 weeks.

Arm type	Experimental
Investigational medicinal product name	Cilofexor 100 mg
Investigational medicinal product code	
Other name	GS-9674
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tablet(s) administered orally once daily, with food

Arm title	OLE Phase: From Cilofexor 30 mg

Arm description:

Following Blinded Study Phase, participants in the Cilofexor 30 mg group, willing to enter OLE Phase received open-label cilofexor 100 mg tablet orally once daily for 96.1 weeks.

Arm type	Experimental
Investigational medicinal product name	Cilofexor 100 mg
Investigational medicinal product code	
Other name	GS-9674
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tablet(s) administered orally once daily, with food

Arm title	OLE Phase: From Placebo

Arm description:

Following Blinded Study Phase, participants in the Placebo group, willing to enter OLE Phase received open-label cilofexor 100 mg tablet orally once daily for 97.3 weeks.

Arm type	Placebo
Investigational medicinal product name	Cilofexor 100 mg
Investigational medicinal product code	
Other name	GS-9674
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tablet(s) administered orally once daily, with food

Number of subjects in period 2	OLE Phase: From Cilofexor 100 mg	OLE Phase: From Cilofexor 30 mg	OLE Phase: From Placebo
Started	23	28	12
Completed	5	3	2
Not completed	18	25	10
Study terminated by sponsor	10	12	6
Adverse event	4	7	3
Withdrew consent	1	1	1
Lost to follow-up	-	1	-
Lack of efficacy	3	4	-

Baseline characteristics

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

Reporting group values	Blinded Study Phase: Cilofexor 100 mg	Blinded Study Phase: Cilofexor 30 mg	Blinded Study Phase: Placebo
Number of subjects	28	30	13
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	54	57	58
standard deviation	± 9.8	± 6.3	± 5.9
Gender categorical			
Units: Subjects			
Female	28	26	12
Male	0	4	1
Race			
Not Permitted = local regulators did not allow collection of race information.			
Units: Subjects			
Asian	2	0	0
Black or African American	0	1	0
White	26	27	13
Not Permitted	0	1	0
Other	0	1	0
Ethnicity			
Not Permitted = local regulators did not allow collection of ethnicity information.			
Units: Subjects			
Hispanic or Latino	1	1	2
Not Hispanic or Latino	26	28	11
Not Permitted	1	1	0

Reporting group values	Total		
Number of subjects	71		
Age categorical			
Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- 		
Gender categorical Units: Subjects			
Female Male	66 5		
Race			
Not Permitted = local regulators did not allow collection of race information.			
Units: Subjects			
Asian Black or African American White Not Permitted Other	2 1 66 1 1		
Ethnicity			
Not Permitted = local regulators did not allow collection of ethnicity information.			
Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Not Permitted	4 65 2		

End points

End points reporting groups

Reporting group title	Blinded Study Phase: Cilofexor 100 mg
Reporting group description:	
Cilofexor 100 mg tablet + placebo to match cilofexor 30 mg tablet orally once daily for 12 weeks.	
Reporting group title	Blinded Study Phase: Cilofexor 30 mg
Reporting group description:	
Cilofexor 30 mg tablet + placebo to match cilofexor 100 mg tablet orally once daily for 12 weeks.	
Reporting group title	Blinded Study Phase: Placebo
Reporting group description:	
Placebo to match cilofexor 100 mg tablet + placebo to match cilofexor 30 mg tablet orally once daily for 12 weeks.	
Reporting group title	OLE Phase: From Cilofexor 100 mg
Reporting group description:	
Following Blinded Study Phase, participants in the Cilofexor 100 mg group, willing to enter Open-Label Extension (OLE) Phase received open-label cilofexor 100 mg tablet orally once daily for 97.4 weeks.	
Reporting group title	OLE Phase: From Cilofexor 30 mg
Reporting group description:	
Following Blinded Study Phase, participants in the Cilofexor 30 mg group, willing to enter OLE Phase received open-label cilofexor 100 mg tablet orally once daily for 96.1 weeks.	
Reporting group title	OLE Phase: From Placebo
Reporting group description:	
Following Blinded Study Phase, participants in the Placebo group, willing to enter OLE Phase received open-label cilofexor 100 mg tablet orally once daily for 97.3 weeks.	

Primary: Percentage of Participants Experiencing Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (TESAEs) in the Blinded Study Phase

End point title	Percentage of Participants Experiencing Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (TESAEs) in the Blinded Study Phase[1]
End point description:	
The Safety Analysis Set included all participants who took at least 1 dose of study drug.	
End point type	Primary
End point timeframe:	
First dose date up to Week 12 + 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	Blinded Study Phase: Cilofexor 100 mg	Blinded Study Phase: Cilofexor 30 mg	Blinded Study Phase: Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	30	13	
Units: percentage of participants				
number (not applicable)				
TEAEs	89.3	76.7	84.6	
TESAEs	0.0	3.3	0.0	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Experiencing TEAEs and TESAEs in the Open-Label Extension (OLE) Phase

End point title	Percentage of Participants Experiencing TEAEs and TESAEs in the Open-Label Extension (OLE) Phase[2]

End point description:

The OLE Analysis Set included all participants who took at least 1 dose of study drug in the OLE Phase.

End point type	Primary

End point timeframe:

First dose date in the OLE phase up to last dose date (Maximum: 97.4 weeks) + 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	OLE Phase: From Cilofexor 100 mg	OLE Phase: From Cilofexor 30 mg	OLE Phase: From Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	28	12	
Units: percentage of participants				
number (not applicable)				
TEAEs	95.7	89.3	100.0	
TESAEs	4.3	0.0	0.0	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Experienced Graded Laboratory Abnormalities in the Blinded Study Phase

End point title	Percentage of Participants Who Experienced Graded Laboratory Abnormalities in the Blinded Study Phase[3]

End point description:

Treatment-emergent laboratory abnormalities were defined as values that increase at least one toxicity grade from baseline. The most severe graded abnormality from all tests was counted for each participant. Participants in the Safety Analysis Set were analyzed.

End point type	Primary

End point timeframe:

First dose date up to Week 12 + 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	Blinded Study Phase: Cilofexor 100 mg	Blinded Study Phase: Cilofexor 30 mg	Blinded Study Phase: Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	30	13	
Units: percentage of participants				
number (not applicable)				
Any Graded Laboratory Abnormality	85.7	86.7	92.3	
Grade 4 or above Laboratory Abnormalities	0.0	3.3	0.0	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Experienced Graded Laboratory Abnormalities in the OLE Phase

End point title	Percentage of Participants Who Experienced Graded Laboratory Abnormalities in the OLE Phase[4]

End point description:

Treatment-emergent laboratory abnormalities were defined as values that increase at least one toxicity grade from
baseline. The most severe graded abnormality from all tests was counted for each participant.
Participants in the OLE Analysis Set were analyzed.

End point type	Primary

End point timeframe:

First dose date in the OLE phase up to last dose date (Maximum: 97.4 weeks) + 30 days

Notes:

[4] - 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	OLE Phase: From Cilofexor 100 mg	OLE Phase: From Cilofexor 30 mg	OLE Phase: From Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	28	12	
Units: percentage of participants				
number (not applicable)				
Any Graded Laboratory Abnormality	91.3	96.4	100.0	
Grade 4 or above Laboratory Abnormalities	0.0	0.0	0.0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Blinded Study Phase: First dose date up to Week 12 + 30 days; Open-Label Extension (OLE) Phase: First dose date in the (OLE) Phase up to last dose date (Maximum: 97.4 weeks) + 30 days

Adverse event reporting additional description:

The Safety Analysis Set for Blinded Study phase included all participants who took at least 1 dose of study drug
in Blinded Study phase and the OLE Analysis Set included all participants who took at least 1 dose of study
drug in OLE phase.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Blinded Study Phase: Cilofexor 100 mg

Reporting group description:

Blinded Study Phase: Cilofexor 100 mg tablet + placebo to match cilofexor 30 mg tablet orally once daily for 12 weeks.

Reporting group title	Blinded Study Phase: Cilofexor 30 mg

Reporting group description:

Blinded Study Phase: Cilofexor 30 mg tablet + placebo to match cilofexor 100 mg tablet orally once daily for 12 weeks.

Reporting group title	Blinded Study Phase: Placebo

Reporting group description:

Blinded Study Phase: Placebo to match cilofexor 100 mg tablet + placebo to match cilofexor 30 mg tablet orally once daily for 12 weeks.

Reporting group title	OLE Phase: From Cilofexor 100 mg

Reporting group description:

OLE Phase: Following Blinded Study Phase, participants in the Cilofexor 100 mg group, willing to enter OLE Phase received open-label cilofexor 100 mg tablet orally once daily for 97.4 weeks.

Reporting group title	OLE Phase: From Cilofexor 30 mg

Reporting group description:

OLE Phase: Following Blinded Study Phase, participants in the Cilofexor 30 mg group, willing to enter OLE Phase received open-label cilofexor 100 mg tablet orally once daily for 96.1 weeks.

Reporting group title	OLE Phase: From Placebo

Reporting group description:

OLE Phase: Following Blinded Study Phase, participants in the Placebo group, willing to enter OLE Phase received open-label cilofexor 100 mg tablet orally once daily for 97.3 weeks.

Serious adverse events	Blinded Study Phase: Cilofexor 100 mg	Blinded Study Phase: Cilofexor 30 mg	Blinded Study Phase: Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 28 (0.00%)	1 / 30 (3.33%)	0 / 13 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 28 (0.00%)	0 / 30 (0.00%)	0 / 13 (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			
Appendicitis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 30 (3.33%)	0 / 13 (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

Serious adverse events	OLE Phase: From Cilofexor 100 mg	OLE Phase: From Cilofexor 30 mg	OLE Phase: From Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 23 (4.35%)	0 / 28 (0.00%)	0 / 12 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 23 (4.35%)	0 / 28 (0.00%)	0 / 12 (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			
Appendicitis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 28 (0.00%)	0 / 12 (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

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

Non-serious adverse events	Blinded Study Phase: Cilofexor 100 mg	Blinded Study Phase: Cilofexor 30 mg	Blinded Study Phase: Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 28 (75.00%)	18 / 30 (60.00%)	11 / 13 (84.62%)
Vascular disorders			
Hypertension			

subjects affected / exposed	0 / 28 (0.00%)	1 / 30 (3.33%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Flushing			
subjects affected / exposed	0 / 28 (0.00%)	0 / 30 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 28 (17.86%)	2 / 30 (6.67%)	3 / 13 (23.08%)
occurrences (all)	5	2	3
Pyrexia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 30 (3.33%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Influenza like illness			
subjects affected / exposed	0 / 28 (0.00%)	0 / 30 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Peripheral swelling			
subjects affected / exposed	0 / 28 (0.00%)	0 / 30 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Cyst			
subjects affected / exposed	0 / 28 (0.00%)	0 / 30 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Suprapubic pain			
subjects affected / exposed	0 / 28 (0.00%)	0 / 30 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 28 (0.00%)	0 / 30 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 28 (0.00%)	0 / 30 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 28 (0.00%)	1 / 30 (3.33%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			

Insomnia			
subjects affected / exposed	0 / 28 (0.00%)	0 / 30 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Personality change			
subjects affected / exposed	0 / 28 (0.00%)	0 / 30 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 28 (0.00%)	0 / 30 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Blood cholesterol increased			
subjects affected / exposed	0 / 28 (0.00%)	0 / 30 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 28 (0.00%)	0 / 30 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Joint injury			
subjects affected / exposed	0 / 28 (0.00%)	0 / 30 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Limb injury			
subjects affected / exposed	0 / 28 (0.00%)	0 / 30 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Procedural anxiety			
subjects affected / exposed	0 / 28 (0.00%)	0 / 30 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 28 (14.29%)	4 / 30 (13.33%)	4 / 13 (30.77%)
occurrences (all)	5	4	4
Somnolence			
subjects affected / exposed	0 / 28 (0.00%)	1 / 30 (3.33%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Tension headache			
subjects affected / exposed	0 / 28 (0.00%)	0 / 30 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1

Hyperaesthesia			
subjects affected / exposed	0 / 28 (0.00%)	0 / 30 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 28 (0.00%)	2 / 30 (6.67%)	0 / 13 (0.00%)
occurrences (all)	0	3	0
Eye disorders			
Dry eye			
subjects affected / exposed	2 / 28 (7.14%)	0 / 30 (0.00%)	0 / 13 (0.00%)
occurrences (all)	2	0	0
Eye pruritus			
subjects affected / exposed	0 / 28 (0.00%)	0 / 30 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 28 (14.29%)	4 / 30 (13.33%)	1 / 13 (7.69%)
occurrences (all)	5	4	1
Nausea			
subjects affected / exposed	3 / 28 (10.71%)	2 / 30 (6.67%)	3 / 13 (23.08%)
occurrences (all)	3	2	3
Abdominal pain			
subjects affected / exposed	1 / 28 (3.57%)	2 / 30 (6.67%)	1 / 13 (7.69%)
occurrences (all)	1	2	1
Constipation			
subjects affected / exposed	2 / 28 (7.14%)	1 / 30 (3.33%)	2 / 13 (15.38%)
occurrences (all)	3	1	2
Vomiting			
subjects affected / exposed	2 / 28 (7.14%)	1 / 30 (3.33%)	0 / 13 (0.00%)
occurrences (all)	2	1	0
Abdominal pain upper			
subjects affected / exposed	1 / 28 (3.57%)	1 / 30 (3.33%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Dry mouth			
subjects affected / exposed	1 / 28 (3.57%)	0 / 30 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal reflux disease			

subjects affected / exposed	1 / 28 (3.57%)	0 / 30 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Abdominal distension			
subjects affected / exposed	0 / 28 (0.00%)	1 / 30 (3.33%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			
subjects affected / exposed	3 / 28 (10.71%)	0 / 30 (0.00%)	0 / 13 (0.00%)
occurrences (all)	3	0	0
Abdominal discomfort			
subjects affected / exposed	0 / 28 (0.00%)	2 / 30 (6.67%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Barrett`s oesophagus			
subjects affected / exposed	0 / 28 (0.00%)	0 / 30 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Gingival bleeding			
subjects affected / exposed	0 / 28 (0.00%)	0 / 30 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	13 / 28 (46.43%)	6 / 30 (20.00%)	3 / 13 (23.08%)
occurrences (all)	14	6	3
Pruritus generalised			
subjects affected / exposed	4 / 28 (14.29%)	0 / 30 (0.00%)	0 / 13 (0.00%)
occurrences (all)	4	0	0
Rash			
subjects affected / exposed	0 / 28 (0.00%)	0 / 30 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Rash maculo-papular			
subjects affected / exposed	1 / 28 (3.57%)	0 / 30 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Rash papular			
subjects affected / exposed	0 / 28 (0.00%)	0 / 30 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			

Myalgia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 30 (3.33%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	0 / 28 (0.00%)	1 / 30 (3.33%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Arthralgia			
subjects affected / exposed	0 / 28 (0.00%)	0 / 30 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	0 / 28 (0.00%)	0 / 30 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Bone pain			
subjects affected / exposed	0 / 28 (0.00%)	0 / 30 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 28 (0.00%)	0 / 30 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 28 (0.00%)	0 / 30 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 28 (14.29%)	5 / 30 (16.67%)	1 / 13 (7.69%)
occurrences (all)	5	6	1
Urinary tract infection			
subjects affected / exposed	2 / 28 (7.14%)	2 / 30 (6.67%)	0 / 13 (0.00%)
occurrences (all)	2	2	0
Influenza			
subjects affected / exposed	2 / 28 (7.14%)	0 / 30 (0.00%)	0 / 13 (0.00%)
occurrences (all)	2	0	0
Sinusitis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 30 (3.33%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			

subjects affected / exposed	0 / 28 (0.00%)	1 / 30 (3.33%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Bronchitis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 30 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Abscess neck			
subjects affected / exposed	0 / 28 (0.00%)	0 / 30 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Carbuncle			
subjects affected / exposed	0 / 28 (0.00%)	0 / 30 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Conjunctivitis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 30 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Infected skin ulcer			
subjects affected / exposed	0 / 28 (0.00%)	0 / 30 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Oral candidiasis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 30 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Skin infection			
subjects affected / exposed	0 / 28 (0.00%)	0 / 30 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	OLE Phase: From Cilofexor 100 mg	OLE Phase: From Cilofexor 30 mg	OLE Phase: From Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 23 (86.96%)	25 / 28 (89.29%)	12 / 12 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 23 (8.70%)	0 / 28 (0.00%)	1 / 12 (8.33%)
occurrences (all)	2	0	1
Flushing			
subjects affected / exposed	0 / 23 (0.00%)	0 / 28 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	3 / 23 (13.04%)	4 / 28 (14.29%)	2 / 12 (16.67%)
occurrences (all)	3	4	2
Pyrexia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 28 (3.57%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Influenza like illness			
subjects affected / exposed	2 / 23 (8.70%)	0 / 28 (0.00%)	0 / 12 (0.00%)
occurrences (all)	3	0	0
Peripheral swelling			
subjects affected / exposed	0 / 23 (0.00%)	2 / 28 (7.14%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Cyst			
subjects affected / exposed	0 / 23 (0.00%)	0 / 28 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Suprapubic pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 28 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 23 (0.00%)	0 / 28 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	2 / 23 (8.70%)	2 / 28 (7.14%)	0 / 12 (0.00%)
occurrences (all)	2	3	0
Rhinorrhoea			
subjects affected / exposed	2 / 23 (8.70%)	0 / 28 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 23 (4.35%)	2 / 28 (7.14%)	0 / 12 (0.00%)
occurrences (all)	1	2	0
Personality change			
subjects affected / exposed	0 / 23 (0.00%)	0 / 28 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1

Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 23 (0.00%)	1 / 28 (3.57%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Blood cholesterol increased			
subjects affected / exposed	0 / 23 (0.00%)	0 / 28 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 23 (4.35%)	0 / 28 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Joint injury			
subjects affected / exposed	0 / 23 (0.00%)	0 / 28 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Limb injury			
subjects affected / exposed	0 / 23 (0.00%)	0 / 28 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Procedural anxiety			
subjects affected / exposed	0 / 23 (0.00%)	0 / 28 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 23 (8.70%)	1 / 28 (3.57%)	0 / 12 (0.00%)
occurrences (all)	2	1	0
Somnolence			
subjects affected / exposed	0 / 23 (0.00%)	0 / 28 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Tension headache			
subjects affected / exposed	0 / 23 (0.00%)	0 / 28 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Hyperaesthesia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 28 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Vertigo			

subjects affected / exposed	2 / 23 (8.70%)	0 / 28 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 23 (0.00%)	2 / 28 (7.14%)	1 / 12 (8.33%)
occurrences (all)	0	2	1
Eye pruritus			
subjects affected / exposed	0 / 23 (0.00%)	0 / 28 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 23 (4.35%)	6 / 28 (21.43%)	4 / 12 (33.33%)
occurrences (all)	1	7	4
Nausea			
subjects affected / exposed	3 / 23 (13.04%)	2 / 28 (7.14%)	2 / 12 (16.67%)
occurrences (all)	3	2	2
Abdominal pain			
subjects affected / exposed	1 / 23 (4.35%)	3 / 28 (10.71%)	1 / 12 (8.33%)
occurrences (all)	1	4	1
Constipation			
subjects affected / exposed	2 / 23 (8.70%)	0 / 28 (0.00%)	2 / 12 (16.67%)
occurrences (all)	2	0	2
Vomiting			
subjects affected / exposed	1 / 23 (4.35%)	1 / 28 (3.57%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Abdominal pain upper			
subjects affected / exposed	1 / 23 (4.35%)	0 / 28 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	2
Dry mouth			
subjects affected / exposed	1 / 23 (4.35%)	2 / 28 (7.14%)	0 / 12 (0.00%)
occurrences (all)	1	2	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 23 (4.35%)	0 / 28 (0.00%)	2 / 12 (16.67%)
occurrences (all)	1	0	2
Abdominal distension			

subjects affected / exposed	0 / 23 (0.00%)	2 / 28 (7.14%)	0 / 12 (0.00%)
occurrences (all)	0	3	0
Dyspepsia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 28 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Abdominal discomfort			
subjects affected / exposed	0 / 23 (0.00%)	0 / 28 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Barrett`s oesophagus			
subjects affected / exposed	0 / 23 (0.00%)	0 / 28 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Gingival bleeding			
subjects affected / exposed	0 / 23 (0.00%)	0 / 28 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	4 / 23 (17.39%)	11 / 28 (39.29%)	6 / 12 (50.00%)
occurrences (all)	5	18	7
Pruritus generalised			
subjects affected / exposed	1 / 23 (4.35%)	1 / 28 (3.57%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Rash			
subjects affected / exposed	2 / 23 (8.70%)	2 / 28 (7.14%)	0 / 12 (0.00%)
occurrences (all)	2	2	0
Rash maculo-papular			
subjects affected / exposed	1 / 23 (4.35%)	0 / 28 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Rash papular			
subjects affected / exposed	0 / 23 (0.00%)	0 / 28 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	3 / 23 (13.04%)	2 / 28 (7.14%)	1 / 12 (8.33%)
occurrences (all)	3	2	1
Pain in extremity			

subjects affected / exposed	2 / 23 (8.70%)	3 / 28 (10.71%)	1 / 12 (8.33%)
occurrences (all)	2	3	1
Arthralgia			
subjects affected / exposed	1 / 23 (4.35%)	3 / 28 (10.71%)	2 / 12 (16.67%)
occurrences (all)	1	3	2
Back pain			
subjects affected / exposed	3 / 23 (13.04%)	0 / 28 (0.00%)	0 / 12 (0.00%)
occurrences (all)	3	0	0
Bone pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 28 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Musculoskeletal pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 28 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Neck pain			
subjects affected / exposed	0 / 23 (0.00%)	1 / 28 (3.57%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 23 (13.04%)	4 / 28 (14.29%)	1 / 12 (8.33%)
occurrences (all)	4	6	1
Urinary tract infection			
subjects affected / exposed	2 / 23 (8.70%)	2 / 28 (7.14%)	2 / 12 (16.67%)
occurrences (all)	2	2	2
Influenza			
subjects affected / exposed	1 / 23 (4.35%)	0 / 28 (0.00%)	2 / 12 (16.67%)
occurrences (all)	1	0	2
Sinusitis			
subjects affected / exposed	1 / 23 (4.35%)	1 / 28 (3.57%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Upper respiratory tract infection			
subjects affected / exposed	1 / 23 (4.35%)	1 / 28 (3.57%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Bronchitis			
subjects affected / exposed	2 / 23 (8.70%)	0 / 28 (0.00%)	1 / 12 (8.33%)
occurrences (all)	2	0	1

Abscess neck			
subjects affected / exposed	0 / 23 (0.00%)	0 / 28 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Carbuncle			
subjects affected / exposed	0 / 23 (0.00%)	0 / 28 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 28 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Infected skin ulcer			
subjects affected / exposed	0 / 23 (0.00%)	0 / 28 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Oral candidiasis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 28 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Skin infection			
subjects affected / exposed	0 / 23 (0.00%)	0 / 28 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 September 2016	• Duration of stable ursodeoxycholic acid (UDCA) use was increased from 6 months to 12 months prior to screening to ensure stability of UDCA-induced alkaline phosphatase (ALP) reductions. • Clarification was added that adults with nonalcoholic steatohepatitis should be excluded. • Additional visits were added for safety monitoring during the OLE phase. • New safety and pharmacokinetic (PK) data from nonclinical studies were added. • The risk/benefit assessment was updated with data from a phase 1 study (GS-US-402-1851) reinforcing the positive benefit/risk ratio. • Magnetic resonance elastography was added as an exploratory measure of liver stiffness. • Inclusion criteria for platelet count, albumin, and creatinine clearance (CLcr) were revised to further ensure adults with advanced liver disease would not be enrolled. • Changes to restrictions on concomitant medications were made based on additional drug-drug interaction study data. • Guidelines for drug-induced liver injury (DILI) monitoring and study drug stopping rules were clarified, and creatine phosphokinase (CPK) testing was added. • Preclinical embryofetal toxicity data were added. Requirements for pregnancy testing and contraceptive use were updated.
21 December 2016	• Final toxicology data were added to support dosing of subjects beyond 12 weeks. • Inclusion criteria were revised to remove CLcr, since serum creatinine was a more appropriate criterion to use in this population. • Concomitant medication guidelines were clarified regarding timing of use of bile acid sequestrants. • Requirements for cirrhosis assessment at screening were clarified. • Frequency of pregnancy testing during the OLE phase was increased.
09 February 2017	• Elevated ALP as a criterion for close observation for drug-induced liver injury (DILI) was removed, since elevated ALP is one of the characteristics of PBC. Criteria for close observation were clarified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
04 September 2019	The study was terminated because of the availability of alternate therapies for primary biliary cholangitis (PBC).	-

Notes:

Limitations and caveats

None reported