Clinical trial results:
A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of Cilofexor in Non-Cirrhotic Subjects With Primary Sclerosing Cholangitis

Summary

EudraCT number	2019-000204-14
Trial protocol	FI BE AT GB DK FR ES IT
Global end of trial date	23 December 2022

Results information

Result version number	v1 (current)
This version publication date	16 December 2023
First version publication date	16 December 2023

Trial information

Trial identification

Sponsor protocol code	GS-US-428-4194

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03890120
WHO universal trial number (UTN)	-
Other trial identifiers	jRCT2080224728: Japan Registry of Clinical Trials

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	23 December 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 November 2022
Global end of trial reached?	Yes
Global end of trial date	23 December 2022
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 whether cilofexor reduces the risk of fibrosis progression among non-cirrhotic 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	27 March 2019
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	Australia: 31
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Canada: 38
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	Finland: 19
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Israel: 11
Country: Number of subjects enrolled	Italy: 23
Country: Number of subjects enrolled	Japan: 27
Country: Number of subjects enrolled	New Zealand: 6
Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	Switzerland: 6
Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	United States: 174

Worldwide total number of subjects	419
EEA total number of subjects	107

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)	395
From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in Europe, North America, Oceania, and Asia.

Pre-assignment

Screening details:

587 participants were screened.

Period 1

Period 1 title	Blinded Treatment Phase (100.3 weeks)
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 (Blinded Phase)

Arm description:

Participants received cilofexor 100 mg tablet, orally, once daily for up to 100.3 weeks.

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

Dosage and administration details:

100 mg tablet administered orally once daily for up to 100.3 weeks.

Arm title	Placebo (Blinded Phase)

Arm description:

Participants received placebo to match cilofexor 100 mg tablet, orally, once daily for up to 98.1 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

placebo to match cilofexor 100 mg tablet administered orally once daily for up to 98.1 weeks.

Number of subjects in period 1	Cilofexor 100 mg (Blinded Phase)	Placebo (Blinded Phase)
Started	278	141
Completed	123	66
Not completed	155	75
Adverse event, non-fatal	17	7

Death	1	-
Pregnancy	-	1
Study terminated by sponsor	119	57
Non-compliance with study drug	-	1
Withdrew consent	12	4
Lost to follow-up	4	1
Investigator's discretion	1	2
Randomized but never treated	1	2

Period 2

Period 2 title	Open-Label Extension Phase (45 weeks)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cilofexor From Cilofexor 100 mg (OLE Phase)

Arm description:

Participants who received cilofexor in blinded phase and had entered the open-label extension (OLE) phase received open-label cilofexor 100 mg tablet, orally, once daily for up to 44.7 weeks.

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

Dosage and administration details:

100 mg tablet administered orally once daily for up to 44.7 weeks.

Arm title	Cilofexor From Placebo (OLE Phase)

Arm description:

Participants who received placebo in blinded phase and had entered the OLE phase received open-label cilofexor 100 mg tablet, orally, once daily for up to 45.0 weeks.

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

Dosage and administration details:

100 mg tablet administered orally once daily for up to 45.0 weeks.

Number of subjects in period 2[1]	Cilofexor From Cilofexor 100 mg (OLE Phase)	Cilofexor From Placebo (OLE Phase)
Started	80	45
Completed	0	0
Not completed	80	45
Adverse event, non-fatal	3	1
Study terminated by sponsor	76	42
Withdrew consent	1	-
Lost to follow-up	-	2

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: Participants who consented to enter the OLE Phase and completed the Blinded Study Phase Week 96 with an evaluable biopsy (noncirrhotic F0, F1, F2, and F3) as determined by the central reader and Blinded Study Phase follow-up visit entered OLE Phase.

Baseline characteristics

Reporting groups	
Reporting group title	Cilofexor 100 mg (Blinded Phase)
Reporting group description:	
Participants received cilofexor 100 mg tablet, orally, once daily for up to 100.3 weeks.	
Reporting group title	Placebo (Blinded Phase)
Reporting group description:	
Participants received placebo to match cilofexor 100 mg tablet, orally, once daily for up to 98.1 weeks.	

Reporting group values	Cilofexor 100 mg (Blinded Phase)	Placebo (Blinded Phase)	Total
Number of subjects	278	141	419
Age categorical Units: Subjects			
18 – 64 Years	260	135	395
65 – 84 Years	18	6	24
Gender categorical Units: Subjects			
Female	107	54	161
Male	171	87	258
Race Units: Subjects			
White	228	117	345
Asian	28	10	38
Black or African American	11	9	20
Unknown or Not Reported	6	5	11
Other or More Than One Race	5	0	5
Ethnicity Units: Subjects			
Hispanic or Latino	11	3	14
Not Hispanic or Latino	259	132	391
Unknown or Not Reported	8	6	14
Alkaline Phosphatase (ALP) Units: units per liter (U/L) arithmetic mean standard deviation	±	±	-
Aspartate Aminotransferase (AST) Units: U/L arithmetic mean standard deviation	±	±	-
Fasting Total Bile Acids Units: micromoles per liter (µmol/L) arithmetic mean standard deviation	±	±	-
Enhanced Liver Fibrosis (ELF™) Test Score			
The Enhanced Liver Fibrosis (ELF™) test is a composite of three serum biomarkers of hepatobiliary fibrosis: hyaluronic acid, procollagen III aminoterminal peptide, and tissue inhibitor of metalloproteinase. A typical range for ELF™ test scores in PSC is between 6 and 14. Higher ELF™ test			

scores are associated with more severe liver disease.			
Units: score on a scale arithmetic mean standard deviation	± 	± 	-
Fibroscan Score			
Change in liver stiffness was measured by FibroScan® scores. FibroScan measures liver scarring by measuring the stiffness of the liver. It's normally between 2 and 6 kPa. Many people with liver disease(s) have a result that's higher than the normal range. Higher scores indicate increased scarring of the liver.			
Units: kilopascals (kPa) arithmetic mean standard deviation	± 	± 	-

Subject analysis sets

Subject analysis set title	Cilofexor 100 mg (Blinded Phase)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received cilofexor 100 mg tablet, orally, once daily for up to 100.3 weeks. Safety Analysis Set included all participants who took at least 1 dose of study drug.

Subject analysis set title	Placebo (Blinded Phase)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received placebo to match cilofexor 100 mg tablet, orally, once daily for up to 98.1 weeks. Participants in the Safety Analysis Set were analyzed.

Subject analysis set title	Cilofexor 100 mg (Blinded Phase)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received cilofexor 100 mg tablet, orally, once daily for up to 100.3 weeks. Participants in the Safety Analysis Set with available data were analyzed.

Subject analysis set title	Placebo (Blinded Phase)
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Subject analysis set description:

Participants received placebo to match cilofexor 100 mg tablet, orally, once daily for up to 98.1 weeks. Participants in the Safety Analysis Set with available data were analyzed.

Subject analysis set title	Cilofexor 100 mg (Blinded Phase)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received cilofexor 100 mg tablet, orally, once daily for up to 100.3 weeks. Participants in the Safety Analysis Set with available data were analyzed.

Subject analysis set title	Placebo (Blinded Phase)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received placebo to match cilofexor 100 mg tablet, orally, once daily for up to 98.1 weeks. Participants in the Safety Analysis Set with available data were analyzed.

Reporting group values	Cilofexor 100 mg (Blinded Phase)	Placebo (Blinded Phase)	Cilofexor 100 mg (Blinded Phase)
Number of subjects	277	139	262
Age categorical Units: Subjects			
18 – 64 Years			
65 – 84 Years			
Gender categorical Units: Subjects			
Female			
Male			
Race Units: Subjects			
White			
Asian			
Black or African American			
Unknown or Not Reported			
Other or More Than One Race			
Ethnicity Units: Subjects			
Hispanic or Latino			
Not Hispanic or Latino			
Unknown or Not Reported			
Alkaline Phosphatase (ALP) Units: units per liter (U/L)			
arithmetic mean	223	243	
standard deviation	± 177.7	± 189.5	±
Aspartate Aminotransferase (AST) Units: U/L			
arithmetic mean	49	51	
standard deviation	± 34.1	± 34.6	±
Fasting Total Bile Acids Units: micromoles per liter (µmol/L)			
arithmetic mean			24.2
standard deviation	±	±	± 37.57
Enhanced Liver Fibrosis (ELF™) Test Score			
The Enhanced Liver Fibrosis (ELF™) test is a composite of three serum biomarkers of hepatobiliary fibrosis: hyaluronic acid, procollagen III aminoterminal peptide, and tissue inhibitor of metalloproteinase. A typical range for ELF™ test scores in PSC is between 6 and 14. Higher ELF™ test scores are associated with more severe liver disease.			
Units: score on a scale			
arithmetic mean			
standard deviation	±	±	±
Fibroscan Score			
Change in liver stiffness was measured by FibroScan® scores. FibroScan measures liver scarring by measuring the stiffness of the liver. It's normally between 2 and 6 kPa. Many people with liver disease			

(s) have a result that's higher than the normal range. Higher scores indicate increased scarring of the liver.			
Units: kilopascals (kPa)			
arithmetic mean			
standard deviation	±	±	±

Reporting group values	Placebo (Blinded Phase)	Cilofexor 100 mg (Blinded Phase)	Placebo (Blinded Phase)
Number of subjects	132	276	137
Age categorical			
Units: Subjects			
18 – 64 Years			
65 – 84 Years			
Gender categorical			
Units: Subjects			
Female			
Male			
Race			
Units: Subjects			
White			
Asian			
Black or African American			
Unknown or Not Reported			
Other or More Than One Race			
Ethnicity			
Units: Subjects			
Hispanic or Latino			
Not Hispanic or Latino			
Unknown or Not Reported			
Alkaline Phosphatase (ALP)			
Units: units per liter (U/L)			
arithmetic mean			
standard deviation	±	±	±
Aspartate Aminotransferase (AST)			
Units: U/L			
arithmetic mean			
standard deviation	±	±	±
Fasting Total Bile Acids			
Units: micromoles per liter (µmol/L)			
arithmetic mean	18.6		
standard deviation	± 22.49	±	±
Enhanced Liver Fibrosis (ELF™) Test Score			
The Enhanced Liver Fibrosis (ELF™) test is a composite of three serum biomarkers of hepatobiliary fibrosis: hyaluronic acid, procollagen III aminoterminal peptide, and tissue inhibitor of metalloproteinase. A typical range for ELF™ test scores in PSC is between 6 and 14. Higher ELF™ test scores are associated with more severe liver disease.			
Units: score on a scale			
arithmetic mean		9.14	9.13
standard deviation	±	± 0.910	± 0.963
Fibroscan Score			
Change in liver stiffness was measured by FibroScan® scores. FibroScan measures liver scarring by measuring the stiffness of the liver. It's normally between 2 and 6 kPa. Many people with liver disease(s) have a result that's higher than the normal range. Higher scores indicate increased scarring			

liver.			
Units: kilopascals (kPa) arithmetic mean standard deviation	±	±	±

Reporting group values	Cilofexor 100 mg (Blinded Phase)	Placebo (Blinded Phase)	
Number of subjects	253	125	
Age categorical Units: Subjects			
18 – 64 Years 65 – 84 Years			
Gender categorical Units: Subjects			
Female Male			
Race Units: Subjects			
White Asian Black or African American Unknown or Not Reported Other or More Than One Race			
Ethnicity Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Unknown or Not Reported			
Alkaline Phosphatase (ALP) Units: units per liter (U/L) arithmetic mean standard deviation	±	±	
Aspartate Aminotransferase (AST) Units: U/L arithmetic mean standard deviation	±	±	
Fasting Total Bile Acids Units: micromoles per liter (µmol/L) arithmetic mean standard deviation	±	±	
Enhanced Liver Fibrosis (ELF™) Test Score			
The Enhanced Liver Fibrosis (ELF™) test is a composite of three serum biomarkers of hepatobiliary fibrosis: hyaluronic acid, procollagen III aminoterminal peptide, and tissue inhibitor of metalloproteinase. A typical range for ELF™ test scores in PSC is between 6 and 14. Higher ELF™ test scores are associated with more severe liver disease.			
Units: score on a scale arithmetic mean standard deviation	±	±	
Fibroscan Score			
Change in liver stiffness was measured by FibroScan® scores. FibroScan measures liver scarring by measuring the stiffness of the liver. It's normally between 2 and 6 kPa. Many people with liver disease(s) have a result that's higher than the normal range. Higher scores indicate increased scarring of the liver.			

Units: kilopascals (kPa)			
arithmetic mean	7.8	8.0	
standard deviation	± 4.91	± 4.07	

End points

End points reporting groups

Reporting group title	Cilofexor 100 mg (Blinded Phase)
Reporting group description:	
Participants received cilofexor 100 mg tablet, orally, once daily for up to 100.3 weeks.	
Reporting group title	Placebo (Blinded Phase)
Reporting group description:	
Participants received placebo to match cilofexor 100 mg tablet, orally, once daily for up to 98.1 weeks.	
Reporting group title	Cilofexor From Cilofexor 100 mg (OLE Phase)
Reporting group description:	
Participants who received cilofexor in blinded phase and had entered the open-label extension (OLE) phase received open-label cilofexor 100 mg tablet, orally, once daily for up to 44.7 weeks.	
Reporting group title	Cilofexor From Placebo (OLE Phase)
Reporting group description:	
Participants who received placebo in blinded phase and had entered the OLE phase received open-label cilofexor 100 mg tablet, orally, once daily for up to 45.0 weeks.	
Subject analysis set title	Cilofexor 100 mg (Blinded Phase)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received cilofexor 100 mg tablet, orally, once daily for up to 100.3 weeks. Safety Analysis Set included all participants who took at least 1 dose of study drug.	

Subject analysis set title	Placebo (Blinded Phase)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received placebo to match cilofexor 100 mg tablet, orally, once daily for up to 98.1 weeks. Participants in the Safety Analysis Set were analyzed.	

Subject analysis set title	Cilofexor 100 mg (Blinded Phase)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received cilofexor 100 mg tablet, orally, once daily for up to 100.3 weeks. Participants in the Safety Analysis Set with available data were analyzed.	

Subject analysis set title	Placebo (Blinded Phase)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received placebo to match cilofexor 100 mg tablet, orally, once daily for up to 98.1 weeks. Participants in the Safety Analysis Set with available data were analyzed.	

Subject analysis set title	Cilofexor 100 mg (Blinded Phase)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received cilofexor 100 mg tablet, orally, once daily for up to 100.3 weeks. Participants in the Safety Analysis Set with available data were analyzed.	

Subject analysis set title	Placebo (Blinded Phase)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received placebo to match cilofexor 100 mg tablet, orally, once daily for up to 98.1 weeks. Participants in the Safety Analysis Set with available data were analyzed.	

Subject analysis set title	Cilofexor 100 mg (Blinded Phase)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received cilofexor 100 mg tablet, orally, once daily for up to 100.3 weeks. Participants in the Safety Analysis Set with available data were analyzed.

Subject analysis set title	Placebo (Blinded Phase)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received placebo to match cilofexor 100 mg tablet, orally, once daily for up to 98.1 weeks. Participants in the Safety Analysis Set with available data were analyzed.

Primary: Percentage of Participants With Progression of Liver Fibrosis at Blinded Phase Week 96

End point title	Percentage of Participants With Progression of Liver Fibrosis at Blinded Phase Week 96

End point description:

Progression of liver fibrosis was defined as having a ≥ 1-stage increase from baseline in fibrosis according to the Ludwig classification at Blinded Phase Week 96. The stages of fibrosis was assessed according to Ludwig classification. Ludwig classification fibrosis stages range from 0 to 4, with higher scores indicating greater fibrosis (0=no fibrosis, 4=cirrhosis). Full Analysis Set included all randomized participants who took at least 1 dose of study drug. Participants in the Full Analysis Set who had nonmissing data at both baseline and Week 96 in the Blinded Study Phase were analyzed.

End point type	Primary

End point timeframe:

Blinded Phase Week 96

End point values	Cilofexor 100 mg (Blinded Phase)	Placebo (Blinded Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	64		
Units: percentage of participants				
number (not applicable)	30.8	32.8		

Statistical analyses

Statistical analysis title	Cilofexor 100 mg vs Placebo
Comparison groups	Cilofexor 100 mg (Blinded Phase) v Placebo (Blinded Phase)
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4186 [1]
Method	Mantel-Haenszel
Parameter estimate	Difference in Percentages
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.2
upper limit	12.3

Notes:

[1] - The difference of cilofexor and placebo,95% confidence interval(CI),and P value(1-sided)were obtained by the stratum-adjusted Mantel-Haenszel (MH) method,with baseline ursodeoxycholic acid (UDCA)use and Ludwig fibrosis stage as stratification factors.

Secondary: Percentage of Participants Who Experienced Treatment-emergent Adverse Events (TEAEs) in The Blinded Phase

End point title	Percentage of Participants Who Experienced Treatment-emergent Adverse Events (TEAEs) in The Blinded Phase

End point description:

An AE was any untoward medical occurrence in a clinical study participant administered a study drug that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a study drug, whether or not the AE is considered related to the study drug. For Blinded Study Phase and OLE Phase, TEAEs were defined as 1 or both of the following: Any 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 and/or any AEs leading to premature discontinuation of study drug. Safety Analysis Set included all participants who took at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

First dose date in the Blinded Phase up to 100.3 weeks plus 30 days

End point values	Cilofexor 100 mg (Blinded Phase)	Placebo (Blinded Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	277	139		
Units: percentage of participants				
number (not applicable)	97.1	95.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Experienced TEAEs in The OLE Phase

End point title	Percentage of Participants Who Experienced TEAEs in The OLE Phase

End point description:

An AE was any untoward medical occurrence in a clinical study participant administered a study drug that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a study drug, whether or not the AE is considered related to the study drug. For Blinded Study Phase and OLE Phase, TEAEs were defined as 1 or both of the following: Any 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 and/or any AEs leading to premature discontinuation of study drug. OLE Analysis Set included all participants who took at least 1 dose of study drug in the OLE Phase.

End point type	Secondary

End point timeframe:

First dose date in the OLE Phase up to 45 weeks plus 30 days

End point values	Cilofexor From Cilofexor 100 mg (OLE Phase)	Cilofexor From Placebo (OLE Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	45		
Units: percentage of participants				
number (not applicable)	66.3	73.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Experienced Treatment-emergent Serious Adverse Events (SAEs) in the Blinded Phase

End point title	Percentage of Participants Who Experienced Treatment-emergent Serious Adverse Events (SAEs) in the Blinded Phase

End point description:

An SAE was defined as an event that, at any dose, results in the following: death, a life-threatening situation; 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	Secondary

End point timeframe:

First dose date in the Blinded Phase up to 100.3 weeks plus 30 days

End point values	Cilofexor 100 mg (Blinded Phase)	Placebo (Blinded Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	277	139		
Units: percentage of participants				
number (not applicable)	19.1	18.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Serum Concentrations of Alkaline Phosphatase (ALP) at Blinded Phase Week 96

End point title	Change From Baseline in Serum Concentrations of Alkaline Phosphatase (ALP) at Blinded Phase Week 96

End point description:

Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Blinded Phase Week 96

End point values	Cilofexor 100 mg (Blinded Phase)	Placebo (Blinded Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	146	74		
Units: units per liter (U/L)				
least squares mean (confidence interval 95%)	0 (-17 to 16)	3 (-19 to 25)		

Statistical analyses

Statistical analysis title	Cilofexor 100 mg vs Placebo
Comparison groups	Cilofexor 100 mg (Blinded Phase) v Placebo (Blinded Phase)
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3884 [2]
Method	ANCOVA
Parameter estimate	Difference in Least Squares Mean (LSM)
Point estimate	-4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28
upper limit	21

Notes:

[2] - The LSM,95% CI and P-value(1-sided) were obtained by an analysis of covariance(ANCOVA)model with change at Week 96 as dependent variable,baseline value of outcome measure,baseline UDCA use, and baseline Ludwig fibrosis stage as independent variables.

Secondary: Percentage of Participants Who Experienced Treatment-emergent SAEs in the OLE Phase

End point title	Percentage of Participants Who Experienced Treatment-emergent SAEs in the OLE Phase

End point description:

An SAE was defined as an event that, at any dose, results in the following: death, a life-threatening situation; 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 OLE Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

First dose date in the OLE Phase up to 45 weeks plus 30 days

End point values	Cilofexor From Cilofexor 100 mg (OLE Phase)	Cilofexor From Placebo (OLE Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	45		
Units: percentage of participants				
number (not applicable)	11.3	2.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Serum Concentrations of Alanine Aminotransferase (ALT) at Blinded Phase Week 96

End point title	Change From Baseline in Serum Concentrations of Alanine Aminotransferase (ALT) at Blinded Phase Week 96
End point description:	
Participants in the Full Analysis Set with available data were analyzed.	
End point type	Secondary
End point timeframe:	
Baseline, Blinded Phase Week 96	

End point values	Cilofexor 100 mg (Blinded Phase)	Placebo (Blinded Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	74		
Units: U/L				
least squares mean (confidence interval 95%)	-13 (-20 to -6)	-3 (-12 to 6)		

Statistical analyses

Statistical analysis title	Cilofexor 100 mg vs Placebo
Comparison groups	Cilofexor 100 mg (Blinded Phase) v Placebo (Blinded Phase)
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.039 [3]
Method	ANCOVA
Parameter estimate	Difference in LSM
Point estimate	-9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-20
upper limit	1

Notes:

[3] - The LSM, 95% CI and P-value (1-sided) were obtained by ANCOVA model to evaluate change at Week 96 as the dependent variable, baseline value of the outcome measure, baseline UDCA use, and baseline Ludwig fibrosis stage as independent variables.

Secondary: Change From Baseline in Serum Concentrations of Fasting Total Bile Acids at Blinded Phase Week 96

End point title	Change From Baseline in Serum Concentrations of Fasting Total Bile Acids at Blinded Phase Week 96

End point description:

Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Blinded Phase Week 96

End point values	Cilofexor 100 mg (Blinded Phase)	Placebo (Blinded Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	74		
Units: micromoles per liter (µmol/L)				
least squares mean (confidence interval 95%)	7.2 (0.9 to 13.5)	9.8 (1.8 to 17.9)		

Statistical analyses

Statistical analysis title	Cilofexor 100 mg vs Placebo
Comparison groups	Cilofexor 100 mg (Blinded Phase) v Placebo (Blinded Phase)
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2845 [4]
Method	ANCOVA
Parameter estimate	Difference in LSM
Point estimate	-2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.6
upper limit	6.4

Notes:

[4] - The LSM, 95% CI and P-value (1-sided) were obtained by ANCOVA model to evaluate change at Week 96 as the dependent variable, baseline value of the outcome measure, baseline UDCA use, and baseline Ludwig fibrosis stage as independent variables.

Secondary: Percentage of Participants With ≥ 25% Relative Reduction in Serum ALP Concentration From Baseline and No Worsening of Fibrosis According to the Ludwig Classification at Blinded Phase Week 96

End point title	Percentage of Participants With ≥ 25% Relative Reduction in Serum ALP Concentration From Baseline and No Worsening of Fibrosis According to the Ludwig Classification at Blinded Phase Week 96

End point description:

The stages of fibrosis was assessed according to Ludwig classification. Ludwig classification fibrosis stages range from 0 to 4, with higher scores indicating greater fibrosis (0=no fibrosis, 4=cirrhosis).The percentage of participants with ≥ 25% reduction in serum ALP Concentration from baseline and no increase in fibrosis according to the Ludwig Classification at Blinded Phase Week 96 was analyzed. Participants in the Full Analysis Set with available data who had nonmissing data at both baseline and Week 96 in the blinded phase were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Blinded Phase Week 96

End point values	Cilofexor 100 mg (Blinded Phase)	Placebo (Blinded Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	61		
Units: percentage of participants				
number (not applicable)	9.8	6.6		

Statistical analyses

Statistical analysis title	Cilofexor 100 mg vs Placebo
Comparison groups	Placebo (Blinded Phase) v Cilofexor 100 mg (Blinded Phase)
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1978 [5]
Method	Mantel-Haenszel
Parameter estimate	Difference in Percentages
Point estimate	4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.3
upper limit	13.5

Notes:

[5] - The difference between cilofexor and Placebo, 95% CI, and the p-value (1-sided) were obtained by the stratum-adjusted MH method, with baseline UDCA use and Ludwig fibrosis stage as stratification factors.

Secondary: Percentage of Participants With Fibrosis Improvement According to the Ludwig Classification at Blinded Phase Week 96

End point title	Percentage of Participants With Fibrosis Improvement According to the Ludwig Classification at Blinded Phase Week 96

End point description:

Fibrosis improvement was defined as ≥ 1-stage decrease from baseline in the Ludwig classification score at Blinded Study Phase Week 96. The stages of fibrosis was assessed according to Ludwig classification. Ludwig classification fibrosis stages range from 0 to 4, with higher scores indicating greater fibrosis (0=no fibrosis, 4=cirrhosis). Participants in the Full Analysis Set with available data who had nonmissing data at both baseline and Week 96 in the blinded phase were analyzed.

End point type	Secondary

End point timeframe:

Blinded Phase Week 96

End point values	Cilofexor 100 mg (Blinded Phase)	Placebo (Blinded Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	64		
Units: percentage of participants				
number (not applicable)	25.6	17.2		

Statistical analyses

Statistical analysis title	Cilofexor 100 mg vs Placebo
Comparison groups	Cilofexor 100 mg (Blinded Phase) v Placebo (Blinded Phase)
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0797 [6]
Method	Mantel-Haenszel
Parameter estimate	Difference in Percentages
Point estimate	8.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	21.2

Notes:

[6] - The difference between cilofexor and Placebo, 95% CI, and the p-value (1-sided) were obtained by the stratum-adjusted MH method, with baseline UDCA use and Ludwig fibrosis stage as stratification factors.

Secondary: Change From Baseline in Primary Sclerosing Cholangitis (PSC) Symptoms - Module 1 based on disease-specific Patient Reported Outcome (PSC-PRO) at Blinded Phase Week 96

End point title	Change From Baseline in Primary Sclerosing Cholangitis (PSC) Symptoms - Module 1 based on disease-specific Patient Reported Outcome (PSC-PRO) at Blinded Phase Week 96

End point description:

The PSC-PRO addressed the severity of common everyday symptoms of PSC (eg, pruritus, fatigue, and right upper quadrant abdominal discomfort); and their functional impact (eg, on physical function, activities of daily living, and work productivity, etc). PSC-PRO module 1 – PSC symptoms contains a total of 12 questions asking about the severity of specific PSC symptoms on a scale of 0 (no symptoms) to 10 (symptoms as bad as you could imagine) with a 24-hour recall period. The total score, which is computed as 12 times the average of nonmissing scores of the 12 questions, can potentially range between 0 and 120, with higher scores indicating more severe symptoms. A positive change from baseline indicates worsening of symptoms. Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Blinded Phase Week 96

End point values	Cilofexor 100 mg (Blinded Phase)	Placebo (Blinded Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274	137		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline	11 (± 11.0)	11 (± 11.8)		
Change at Blinded Phase Wk 96 (N=163, 78)	1 (± 9.0)	0 (± 6.8)		

Statistical analyses

Statistical analysis title	Cilofexor 100 mg vs Placebo
Comparison groups	Cilofexor 100 mg (Blinded Phase) v Placebo (Blinded Phase)
Number of subjects included in analysis	411
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7275 [7]
Method	ANCOVA
Parameter estimate	Difference in LSM
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	3

Notes:

[7] - The LSM, 95% CI and P-value (1-sided) were obtained by ANCOVA model to evaluate change at Week 96 as the dependent variable, baseline value of the outcome measure, baseline UDCA use, and baseline Ludwig fibrosis stage as independent variables.

Secondary: Change From Baseline in Enhanced Liver Fibrosis (ELF™) Test Score at Blinded Phase Week 96

End point title	Change From Baseline in Enhanced Liver Fibrosis (ELF™) Test Score at Blinded Phase Week 96

End point description:

The Enhanced Liver Fibrosis (ELF™) test is a composite of three serum biomarkers of hepatobiliary fibrosis: hyaluronic acid, procollagen III aminoterminal peptide, and tissue inhibitor of metalloproteinase. A typical range for ELF™ test scores in PSC is between 6 and 14. Higher ELF™ test scores are associated with more severe liver disease. A positive change from baseline indicated worsening of fibrosis. Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Blinded Phase Week 96

End point values	Cilofexor 100 mg (Blinded Phase)	Placebo (Blinded Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	78		
Units: score on a scale				
least squares mean (confidence interval 95%)	0.27 (0.16 to 0.38)	0.30 (0.15 to 0.45)		

Statistical analyses

Statistical analysis title	Cilofexor 100 mg vs Placebo
Comparison groups	Cilofexor 100 mg (Blinded Phase) v Placebo (Blinded Phase)
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3636 [8]
Method	ANCOVA
Parameter estimate	Difference in LSM
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.14

Notes:

[8] - The LSM, 95% CI and P-value (1-sided) were obtained by ANCOVA model to evaluate change at Week 96 as the dependent variable, baseline value of the outcome measure, baseline UDCA use, and baseline Ludwig fibrosis stage as independent variables.

Secondary: Change From Baseline in Liver Stiffness by FibroScan® at Blinded Phase Week 96

End point title	Change From Baseline in Liver Stiffness by FibroScan® at Blinded Phase Week 96

End point description:

Change in liver stiffness was measured by FibroScan® scores. FibroScan measures liver scarring by measuring the stiffness of the liver. It's normally between 2 and 6 kPa. Many people with liver disease(s) have a result that's higher than the normal range. Higher scores indicate increased scarring of the liver. A positive change from baseline indicates severe liver disease(s). Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Blinded Phase Week 96

End point values	Cilofexor 100 mg (Blinded Phase)	Placebo (Blinded Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	73		
Units: kilopascals (kPa)				
least squares mean (confidence interval 95%)	2.4 (1.2 to 3.6)	2.8 (1.1 to 4.4)		

Statistical analyses

Statistical analysis title	Cilofexor 100 mg vs Placebo
Comparison groups	Cilofexor 100 mg (Blinded Phase) v Placebo (Blinded Phase)
Number of subjects included in analysis	227
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3595 [9]
Method	ANCOVA
Parameter estimate	Difference in LSM
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	1.5

Notes:

[9] - The LSM, 95% CI and P-value (1-sided) were obtained by ANCOVA model to evaluate change at Week 96 as the dependent variable, baseline value of the outcome measure, baseline UDCA use, and baseline Ludwig fibrosis stage as independent variables.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality: Randomization up to 3.4 years; Adverse events: Blinded Phase: First dose date in the Blinded Phase up to 100.3 weeks plus 30 days; Open-Label Extension (OLE) Phase: First dose date in the OLE Phase up to 45 weeks plus 30 days

Adverse event reporting additional description:

All-cause mortality: All Randomized Analysis Set included all participants who were randomized in the study.
Adverse Events: 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	25.1

Reporting groups

Reporting group title	Cilofexor 100 mg (Blinded Phase)

Reporting group description:

Participants received cilofexor 100 mg tablet, orally, once daily for up to 100.3 weeks.

Reporting group title	Placebo (Blinded Phase)

Reporting group description:

Participants received placebo to match cilofexor 100 mg tablet, orally, once daily for up to 98.1 weeks.

Reporting group title	Cilofexor From Cilofexor 100 mg (OLE Phase)

Reporting group description:

Participants who received cilofexor in blinded phase and had entered the OLE phase received open-label cilofexor 100 mg tablet, orally, once daily for up to 44.7 weeks.

Reporting group title	Cilofexor From Placebo (OLE Phase)

Reporting group description:

Participants who received placebo in blinded phase and had entered the OLE phase received open-label cilofexor 100 mg tablet, orally, once daily for up to 45.0 weeks.

Serious adverse events	Cilofexor 100 mg (Blinded Phase)	Placebo (Blinded Phase)	Cilofexor From Cilofexor 100 mg (OLE Phase)
Total subjects affected by serious adverse events			
subjects affected / exposed	53 / 277 (19.13%)	26 / 139 (18.71%)	9 / 80 (11.25%)
number of deaths (all causes)	2	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cholangiocarcinoma			
subjects affected / exposed	0 / 277 (0.00%)	2 / 139 (1.44%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of colon			

subjects affected / exposed	0 / 277 (0.00%)	0 / 139 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer metastatic			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Lung adenocarcinoma			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Gastric cancer			
subjects affected / exposed	0 / 277 (0.00%)	1 / 139 (0.72%)	0 / 80 (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
Gallbladder cancer			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Renal neoplasm			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Marginal zone lymphoma			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 277 (0.00%)	1 / 139 (0.72%)	0 / 80 (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
Surgical and medical procedures			

Cholecystectomy			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Colorectostomy			
subjects affected / exposed	0 / 277 (0.00%)	0 / 139 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver transplant			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Ligament operation			
subjects affected / exposed	0 / 277 (0.00%)	1 / 139 (0.72%)	0 / 80 (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
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 277 (1.44%)	1 / 139 (0.72%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 277 (0.00%)	1 / 139 (0.72%)	0 / 80 (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
Chills			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Immune system disorders			
Anaphylactoid reaction			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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

Investigations			
General physical condition abnormal			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 277 (0.00%)	1 / 139 (0.72%)	0 / 80 (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
Endoscopic retrograde ~ cholangiopancreatography			
subjects affected / exposed	1 / 277 (0.36%)	1 / 139 (0.72%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
International normalised ratio ~ increased			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Hepatic enzyme abnormal			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Injury, poisoning and procedural complications			
Post procedural complication			
subjects affected / exposed	0 / 277 (0.00%)	1 / 139 (0.72%)	0 / 80 (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
Gastrointestinal procedural ~ complication			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Clavicle fracture			

subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Ligament rupture			
subjects affected / exposed	1 / 277 (0.36%)	1 / 139 (0.72%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Procedural pain			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 277 (0.00%)	1 / 139 (0.72%)	0 / 80 (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
Dizziness			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Headache			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Peroneal nerve palsy			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Migraine with aura			

subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Syncope			
subjects affected / exposed	0 / 277 (0.00%)	0 / 139 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 277 (0.00%)	1 / 139 (0.72%)	0 / 80 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 277 (1.08%)	0 / 139 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Crohn's disease			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Abdominal pain upper			
subjects affected / exposed	2 / 277 (0.72%)	0 / 139 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea haemorrhagic			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Gastritis			

subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Ileus			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Large intestine polyp			
subjects affected / exposed	0 / 277 (0.00%)	1 / 139 (0.72%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Obstructive pancreatitis			
subjects affected / exposed	0 / 277 (0.00%)	0 / 139 (0.00%)	1 / 80 (1.25%)
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	0 / 277 (0.00%)	1 / 139 (0.72%)	0 / 80 (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
Pancreatitis acute			
subjects affected / exposed	0 / 277 (0.00%)	1 / 139 (0.72%)	0 / 80 (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
Pouchitis			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Hepatobiliary disorders			
Cholangitis			

subjects affected / exposed	10 / 277 (3.61%)	7 / 139 (5.04%)	2 / 80 (2.50%)
occurrences causally related to treatment / all	1 / 17	1 / 10	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct stenosis			
subjects affected / exposed	1 / 277 (0.36%)	2 / 139 (1.44%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	4 / 277 (1.44%)	0 / 139 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	2 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis acute			
subjects affected / exposed	4 / 277 (1.44%)	0 / 139 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct stone			
subjects affected / exposed	2 / 277 (0.72%)	0 / 139 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	2 / 277 (0.72%)	0 / 139 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	2 / 277 (0.72%)	0 / 139 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis sclerosing			
subjects affected / exposed	2 / 277 (0.72%)	0 / 139 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			

subjects affected / exposed	1 / 277 (0.36%)	1 / 139 (0.72%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice cholestatic			
subjects affected / exposed	1 / 277 (0.36%)	1 / 139 (0.72%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary colic			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Biliary dilatation			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Hepatic haematoma			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Haemorrhagic cholecystitis			
subjects affected / exposed	0 / 277 (0.00%)	1 / 139 (0.72%)	0 / 80 (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
Drug-induced liver injury			
subjects affected / exposed	0 / 277 (0.00%)	1 / 139 (0.72%)	0 / 80 (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
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	2 / 277 (0.72%)	0 / 139 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Nephrolithiasis			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Appendicitis			
subjects affected / exposed	0 / 277 (0.00%)	1 / 139 (0.72%)	0 / 80 (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
Cholangitis infective			
subjects affected / exposed	0 / 277 (0.00%)	1 / 139 (0.72%)	0 / 80 (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
Febrile infection			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Gastroenteritis			
subjects affected / exposed	0 / 277 (0.00%)	0 / 139 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis salmonella			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Infection			
subjects affected / exposed	0 / 277 (0.00%)	1 / 139 (0.72%)	0 / 80 (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
Klebsiella infection			

subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Liver abscess			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Lower respiratory tract infection			
subjects affected / exposed	0 / 277 (0.00%)	1 / 139 (0.72%)	0 / 80 (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
Meningitis			
subjects affected / exposed	0 / 277 (0.00%)	1 / 139 (0.72%)	0 / 80 (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
Pharyngitis			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Pneumonia			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Post procedural sepsis			
subjects affected / exposed	0 / 277 (0.00%)	1 / 139 (0.72%)	0 / 80 (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
Postoperative abscess			
subjects affected / exposed	0 / 277 (0.00%)	1 / 139 (0.72%)	0 / 80 (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
Wound infection			

subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Streptococcal sepsis			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Soft tissue infection			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Sepsis			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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
Metabolism and nutrition disorders			
Type 1 diabetes mellitus			
subjects affected / exposed	1 / 277 (0.36%)	0 / 139 (0.00%)	0 / 80 (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 From Placebo (OLE Phase)		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 45 (2.22%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cholangiocarcinoma			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Adenocarcinoma of colon			

subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Breast cancer metastatic				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung adenocarcinoma				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric cancer				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gallbladder cancer				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal neoplasm				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Marginal zone lymphoma				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Hypotension				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				

Cholecystectomy				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colorectostomy				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Liver transplant				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ligament operation				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Pyrexia				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chills				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Anaphylactoid reaction				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Investigations			
General physical condition abnormal			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Alanine aminotransferase increased			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endoscopic retrograde ~ cholangiopancreatography			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
International normalised ratio ~ increased			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic enzyme abnormal			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Post procedural complication			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal procedural ~ complication			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Clavicle fracture			

subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ligament rupture				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post procedural haemorrhage				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Procedural pain				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebrovascular accident				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peroneal nerve palsy				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Migraine with aura				

subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Crohn's disease				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea haemorrhagic				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastritis				

subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large intestine polyp				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Obstructive pancreatitis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis acute				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pouchitis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholangitis				

subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bile duct stenosis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystitis acute				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholangitis acute				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bile duct stone				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperbilirubinaemia				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholelithiasis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholangitis sclerosing				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Jaundice				

subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Jaundice cholestatic				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Biliary colic				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Biliary dilatation				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic haematoma				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhagic cholecystitis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Drug-induced liver injury				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Pruritus				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				

Nephrolithiasis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Abdominal abscess				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholangitis infective				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Febrile infection				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis salmonella				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Klebsiella infection				

subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Liver abscess				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Meningitis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pharyngitis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post procedural sepsis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Postoperative abscess				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Wound infection				

subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Streptococcal sepsis			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Soft tissue infection			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 45 (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)	Placebo (Blinded Phase)	Cilofexor From Cilofexor 100 mg (OLE Phase)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	232 / 277 (83.75%)	109 / 139 (78.42%)	34 / 80 (42.50%)
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	8 / 277 (2.89%)	7 / 139 (5.04%)	0 / 80 (0.00%)
occurrences (all)	10	8	0
Nervous system disorders			
Headache			
subjects affected / exposed	32 / 277 (11.55%)	18 / 139 (12.95%)	1 / 80 (1.25%)
occurrences (all)	44	21	1

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	34 / 277 (12.27%)	24 / 139 (17.27%)	3 / 80 (3.75%)
occurrences (all)	37	28	3
Pyrexia			
subjects affected / exposed	33 / 277 (11.91%)	9 / 139 (6.47%)	3 / 80 (3.75%)
occurrences (all)	48	12	3
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	40 / 277 (14.44%)	20 / 139 (14.39%)	1 / 80 (1.25%)
occurrences (all)	50	22	1
Abdominal pain			
subjects affected / exposed	38 / 277 (13.72%)	17 / 139 (12.23%)	1 / 80 (1.25%)
occurrences (all)	52	20	1
Nausea			
subjects affected / exposed	34 / 277 (12.27%)	16 / 139 (11.51%)	4 / 80 (5.00%)
occurrences (all)	42	19	4
Diarrhoea			
subjects affected / exposed	21 / 277 (7.58%)	11 / 139 (7.91%)	2 / 80 (2.50%)
occurrences (all)	24	12	2
Abdominal distension			
subjects affected / exposed	9 / 277 (3.25%)	9 / 139 (6.47%)	0 / 80 (0.00%)
occurrences (all)	10	9	0
Vomiting			
subjects affected / exposed	12 / 277 (4.33%)	7 / 139 (5.04%)	1 / 80 (1.25%)
occurrences (all)	12	7	1
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	135 / 277 (48.74%)	50 / 139 (35.97%)	14 / 80 (17.50%)
occurrences (all)	184	58	14
Rash			
subjects affected / exposed	16 / 277 (5.78%)	7 / 139 (5.04%)	1 / 80 (1.25%)
occurrences (all)	17	8	2
Psychiatric disorders			
Insomnia			

subjects affected / exposed	14 / 277 (5.05%)	2 / 139 (1.44%)	1 / 80 (1.25%)
occurrences (all)	15	2	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	15 / 277 (5.42%)	14 / 139 (10.07%)	2 / 80 (2.50%)
occurrences (all)	18	14	2
Back pain			
subjects affected / exposed	21 / 277 (7.58%)	8 / 139 (5.76%)	3 / 80 (3.75%)
occurrences (all)	22	9	3
Infections and infestations			
Covid-19			
subjects affected / exposed	65 / 277 (23.47%)	26 / 139 (18.71%)	11 / 80 (13.75%)
occurrences (all)	68	27	11
Nasopharyngitis			
subjects affected / exposed	15 / 277 (5.42%)	12 / 139 (8.63%)	0 / 80 (0.00%)
occurrences (all)	22	13	0
Upper respiratory tract infection			
subjects affected / exposed	14 / 277 (5.05%)	7 / 139 (5.04%)	1 / 80 (1.25%)
occurrences (all)	17	8	1
Urinary tract infection			
subjects affected / exposed	8 / 277 (2.89%)	5 / 139 (3.60%)	5 / 80 (6.25%)
occurrences (all)	11	5	5

Non-serious adverse events	Cilofexor From Placebo (OLE Phase)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 45 (53.33%)		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			

Fatigue subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	 0 / 45 (0.00%) 0 2 / 45 (4.44%) 4		
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Abdominal distension subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 2 / 45 (4.44%) 2 0 / 45 (0.00%) 0 0 / 45 (0.00%) 0 1 / 45 (2.22%) 1 2 / 45 (4.44%) 2 0 / 45 (0.00%) 0		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 11 / 45 (24.44%) 13 0 / 45 (0.00%) 0		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 2 / 45 (4.44%) 2		
Musculoskeletal and connective tissue			

disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all)	 0 / 45 (0.00%) 0 0 / 45 (0.00%) 0		
Infections and infestations Covid-19 subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	 11 / 45 (24.44%) 11 1 / 45 (2.22%) 1 2 / 45 (4.44%) 2 0 / 45 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 March 2019	- In various sections within the protocol, liver stiffness by FibroScan® will be assessed if available. - In various sections within the protocol, sample size power was calculated using the "Pearson's" Chi-square test for clarity. - In various sections within the protocol, "study procedures manual" and "study reference binder" were revised to "Site Operations Manual" for alignment.
23 October 2019	- In various sections within the protocol, GS-9674 was updated to use the study drug name cilofexor, abbreviated as CILO
07 April 2020	- Clarified that IBD includes ulcerative colitis, Crohn's disease, and indeterminant colitis - Clarified that Partial Mayo score collection is not required for subjects using external ostomy bags - The term study medication has been updated to study drug - The term medicinal product has been updated to investigational product - Appendix 2.: Study Procedures Table and the associated footnotes updated to align with the key changes
30 June 2021	- Section 1.2.7 and 1.2.8 have been updated with final results from study GS-US-428-4025. - The terminology for the Blinded Study Phase was added and the corresponding sections were updated accordingly. - The protocol synopsis and the study procedure table(s) were updated to align with the updates to the body of the protocol. - Administrative changes throughout, including abbreviations, updates to terminology, updates to section headings, consistency with revised protocol template, language and additional minor edits.
16 March 2022	- Objectives and endpoints were updated (Section 2): • Time point "Blinded Study Phase Week 96" was added to the primary objective (Sections 2 and 8.1.1). • Evaluation of GGT was moved from secondary objectives/endpoints to exploratory objectives/endpoints (Sections 2, 8.1.1, 8.1.3, and 8.5.2). • Secondary objective/endpoint "To evaluate changes in liver fibrosis including hepatic collagen content and progression to cirrhosis at Blinded Study Phase Week 96" was moved to the exploratory objectives/endpoints" (Sections 2, 8.1.1, and 8.5.2). • Text updated to clarify that change in primary sclerosing cholangitis (PSC) symptoms will be evaluated based on the disease-specific PSC-patient-reported outcome (PSC-PRO) Module 1 at Blinded Study Phase Week 96 (Sections 2, 8.1.1, 8.1.3, and 8.5.2). - Text added to clarify that if the Blinded Study Phase follow-up visit and the OLE Phase baseline/Day 1 visit occur on the same day, study assessment procedures should be performed according to the OLE Phase baseline/Day 1 visit (Sections 3.1, and 6.4.7).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
26 September 2022	Following recommendation of the external Data Monitoring Committee, after it reviewed the results of a planned interim futility analysis.	-

Notes:

Limitations and caveats

None reported