



Clinical trial results:

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

Summary

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

Results information

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

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | GS-US-428-4025 |
|-----------------------|----------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Gilead Sciences |
| Sponsor organisation address | 333 Lakeside Drive, Foster City, CA, United States, 94404 |
| Public contact | Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com |
| Scientific contact | Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Interim |
| Date of interim/final analysis | 26 March 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 28 February 2018 |
| Global end of trial reached? | No |

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

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

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

Notes:

Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |

| | |
|---------------------------|----|
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 52 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

105 participants were screened.

Period 1

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

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|------------------|
| Arm title | Cilofexor 100 mg |
|------------------|------------------|

Arm description:

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

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

Dosage and administration details:

100 mg administered once daily

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

Dosage and administration details:

Administered once daily

| | |
|------------------|-----------------|
| Arm title | Cilofexor 30 mg |
|------------------|-----------------|

Arm description:

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

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

Dosage and administration details:

30 mg administered once daily

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

| | |
|------------------------------------|----------|
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Administered once daily | |

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

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

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

Dosage and administration details:

Administered once daily

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

Dosage and administration details:

Administered once daily

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

Period 2

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

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

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

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

Notes:

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

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

Baseline characteristics

Reporting groups

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

| Reporting group values | Cilofexor 100 mg | Cilofexor 30 mg | Placebo |
|------------------------|------------------|-----------------|---------|
| Number of subjects | 22 | 20 | 10 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|---------------------------|-------|--------|--------|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 42 | 46 | 42 |
| standard deviation | ± 8.6 | ± 12.1 | ± 10.9 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 11 | 6 | 5 |
| Male | 11 | 14 | 5 |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 0 | 3 | 0 |
| Not Hispanic or Latino | 21 | 17 | 9 |
| Unknown or Not Reported | 1 | 0 | 1 |
| Race | | | |
| Units: Subjects | | | |
| Asian | 0 | 2 | 1 |
| Black or African American | 4 | 3 | 1 |
| White | 17 | 15 | 7 |
| Not Permitted | 0 | 0 | 1 |
| Other | 1 | 0 | 0 |

| Reporting group values | Total | | |
|------------------------|-------|--|--|
| Number of subjects | 52 | | |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|--------------------|---|--|--|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |

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

End points

End points reporting groups

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

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

| | |
|---|---|
| End point title | Percentage of Participants Experiencing Treatment-Emergent Adverse Events During the Blinded Phase ^[1] |
| End point description: Treatment-emergent adverse events occurring during the Blinded Phase were defined as 1 or both of the following: 1) Any adverse events (AEs) with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug in the Blinded Phase (and before the first dosing date in the Open Label Extension (OLE) Phase), or 2) Any AEs leading to premature discontinuation of study drug in the Blinded Phase. Safety Analysis Set included all participants who took at least 1 dose of study drug. | |
| End point type | Primary |
| End point timeframe: Up to 12 weeks plus 30 days | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical comparison was planned or performed.

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to 12 weeks plus 30 days

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical comparison was planned or performed.

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to 12 weeks plus 30 days

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical comparison was planned or performed.

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to the Week 12 Data Cut

Adverse event reporting additional description:

Safety Analysis Set included all participants who took at least 1 dose of study drug.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------------------------|
| Reporting group title | Cilofexor 100 mg (Blinded Phase) |
|-----------------------|----------------------------------|

Reporting group description:

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

| | |
|-----------------------|---------------------------------|
| Reporting group title | Cilofexor 30 mg (Blinded Phase) |
|-----------------------|---------------------------------|

Reporting group description:

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

| | |
|-----------------------|-------------------------|
| Reporting group title | Placebo (Blinded Phase) |
|-----------------------|-------------------------|

Reporting group description:

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

| | |
|-----------------------|-------------------------------------|
| Reporting group title | Cilofexor 100 mg (Open Label Phase) |
|-----------------------|-------------------------------------|

Reporting group description:

Cilofexor 100 mg tablet once daily for an additional 96 weeks

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

| | | | |
|---|----------------|----------------|----------------|
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 20 (0.00%) | 0 / 10 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 20 (0.00%) | 0 / 10 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 20 (0.00%) | 0 / 10 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 20 (0.00%) | 0 / 10 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 20 (0.00%) | 0 / 10 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 30 September 2016 | <ul style="list-style-type: none">• Increased number of months of prior ursodeoxycholic acid (UDCA) use to allow longer duration for UDCA induced reductions in alkaline phosphatase to appear.• Added clarity that participants with nonalcoholic steatohepatitis (NASH) should be excluded and definition of inflammatory bowel disease (IBD) and liver fibrosis scoring updated.• Additional visits added for safety monitoring in the Open Label Extension.• Updated with additional available safety and PK data.• Inclusion criteria updated to further ensure participants with more advanced liver disease/cirrhosis and IBD are not included.• Prohibited concomitant medications updated based on additional available drug-drug interaction (DDI) data.• Updated to add exclusion of chronic antibiotic use for the treatment of PSC.• Clarified that rescreeing once is allowed.• Updated contraception requirements section based on DDI and pre-clinical embryofetal toxicity data now available. |
| 21 December 2016 | <ul style="list-style-type: none">• Language added for clarification that direct bilirubin will be used instead of total bilirubin in FibroSURE/FibroTest® calculations in participants with Gilbert's syndrome or hemolysis, and that in subjects with FibroSURE/FibroTest® ≥ 0.75 may be included if a biopsy within 12 months of screening has excluded cirrhosis.• Updated to reflect final non-clinical toxicology data to support dosing beyond 12 weeks.• Updated inclusion criteria from creatinine clearance to serum creatinine.• Language added to clarify that study drug should not be dosed within 4 hours of dosing with bile acid sequestrants.• Language added to clarify retesting/rescreeing eligibility for subjects.• Clarified that cirrhosis assessments include review of historical information including liver histology and FibroScan results if available.• Language added for pregnancy requirement for clarification. |
| 09 February 2017 | <ul style="list-style-type: none">• Updated section on toxicity management observation for drug induced liver injury (DILI) for clarification and removed elevated serum alkaline phosphatase (ALP) as one of the close observation criteria. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

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

Notes: