



## Clinical trial results:

**A two-part, randomized, placebo controlled, double blind, multicenter, Phase 3 study to evaluate the efficacy and safety of linerixibat for the treatment of cholestatic pruritus in participants with primary biliary cholangitis (PBC).**

### Summary

EudraCT number	2021-000007-21
Trial protocol	FR BE IT CZ GR ES
Global end of trial date	20 December 2024

### Results information

Result version number	v1 (current)
This version publication date	18 July 2025
First version publication date	18 July 2025

### Trial information

#### Trial identification

Sponsor protocol code	212620
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04950127
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	Great West Road, Brentford, Middlesex, United Kingdom, TW8 9GS
Public contact	GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.com
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.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	11 February 2025
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	20 December 2024
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To investigate the effect of treatment with oral linerixibat compared with placebo on itch in PBC patients with cholestatic pruritus over 24 weeks (Part A).

Protection of trial subjects:

None

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 August 2021
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	Argentina: 24
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Brazil: 12
Country: Number of subjects enrolled	Bulgaria: 7
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	China: 38
Country: Number of subjects enrolled	Czechia: 7
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Israel: 6
Country: Number of subjects enrolled	Italy: 15
Country: Number of subjects enrolled	Japan: 34
Country: Number of subjects enrolled	Mexico: 13
Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	Russian Federation: 3
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	United States: 36
Worldwide total number of subjects	238
EEA total number of subjects	48

Notes:

<b>Subjects enrolled per age group</b>	
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)	178
From 65 to 84 years	60
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

A total of 238 participants from Europe, North America, Latin America and Asia were enrolled and randomized.

### Pre-assignment

Screening details:

This study was conducted in 2 parts: Part A, Part B. Participants were randomized in 1:1:1:1 ratio to receive either: linerixibat 40 milligram(mg) twice a day(BID) in Part A and Part B, linerixibat 40mg twice a day(BID) in Part A and placebo in Part B, placebo in Part A and Part B, or placebo in Part A and linerixibat 40mg twice a day(BID) in Part B

### Period 1

Period 1 title	Part A (Day 1 to Week 24)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Part A: Linerixibat 40 milligrams (mg)

Arm description:

Participants were randomized to receive linerixibat 40 mg tablet orally twice a day (BID) in Part A (up to Week 24)

Arm type	Experimental
Investigational medicinal product name	Linerixibat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet taken twice daily

<b>Arm title</b>	Part A: Placebo
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Arm description:

Participants were randomized to receive Placebo orally twice a day (BID) in Part A (up to Week 24).

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

Dosage and administration details:

1 tablet taken twice daily

Number of subjects in period 1	Part A: Linerixibat 40 milligrams (mg)	Part A: Placebo
Started	119	119
Safety Population	119	118
Completed	103	108
Not completed	16	11
Physician decision	3	2
Consent withdrawn by subject	9	7
Adverse event, non-fatal	4	2

## Period 2

Period 2 title	Part B (Week 24 to Week 32)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

## Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Part B: Placebo in Part A and Part B

### Arm description:

Participants who were randomized to receive Placebo (up to Week 24) orally twice a day (BID) in Part A, continued to receive Placebo (from Week 24 to Week 32) orally twice a day (BID) in Part B.

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

### Dosage and administration details:

1 tablet taken twice daily

<b>Arm title</b>	Part B: Placebo in Part A and Linerixibat 40 mg in Part B
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### Arm description:

Participants who were randomized to receive Placebo (up to Week 24) orally twice a day (BID) in Part A, switched to receive linerixibat 40 mg tablet orally twice a day (BID) (from Week 24 to Week 32) in Part B.

Arm type	Placebo in Part A and Linerixibat in Part B
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

### Dosage and administration details:

1 tablet taken twice daily.

Investigational medicinal product name	Linerixibat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet taken twice daily

<b>Arm title</b>	Part B: Linerixibat 40 mg in Part A and Placebo in Part B
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Arm description:

Participants who were randomized to receive linerixibat 40 mg tablet orally BID (up to Week 24) in Part A, switched to receive Placebo (from Week 24 to Week 32) orally twice a day (BID) in Part B.

Arm type	Linerixibat in Part A and Placebo in Part B
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet taken twice daily

Investigational medicinal product name	Linerixibat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet taken twice daily

<b>Arm title</b>	Part B: Linerixibat 40 mg in Part A and Part B
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Arm description:

Participants who were randomized to receive linerixibat 40 mg tablet orally twice a day (BID) (up to Week 24) in Part A, continued to receive linerixibat 40 mg twice a day (BID) (from Week 24 to Week 32) in Part B.

Arm type	Experimental
Investigational medicinal product name	Linerixibat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet taken twice daily

Number of subjects in period 2	Part B: Placebo in Part A and Part B	Part B: Placebo in Part A and Linerixibat 40 mg in Part B	Part B: Linerixibat 40 mg in Part A and Placebo in Part B
Started	55	53	49
Safety Population	53 <sup>[1]</sup>	52 <sup>[2]</sup>	46 <sup>[3]</sup>
Completed	55	53	49
Not completed	0	0	0
Consent withdrawn by subject	-	-	-

Physician decision	-	-	-
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Number of subjects in period 2	Part B: Linerixibat 40 mg in Part A and Part B
Started	54
Safety Population	45 <sup>[4]</sup>
Completed	49
Not completed	5
Consent withdrawn by subject	4
Physician decision	1

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Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The Safety Population includes participants who received at least 1 dose in Part B.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The Safety Population includes participants who received at least 1 dose in Part B.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The Safety Population includes participants who received at least 1 dose in Part B.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The Safety Population includes participants who received at least 1 dose in Part B.

## Baseline characteristics

### Reporting groups

Reporting group title	Part A: Linerixibat 40 milligrams (mg)
Reporting group description: Participants were randomized to receive linerixibat 40 mg tablet orally twice a day (BID) in Part A (up to Week 24)	
Reporting group title	Part A: Placebo
Reporting group description: Participants were randomized to receive Placebo orally twice a day (BID) in Part A (up to Week 24).	

Reporting group values	Part A: Linerixibat 40 milligrams (mg)	Part A: Placebo	Total
Number of subjects	119	119	238
Age Categorical			
Units: Participants			
18-49 Years	42	30	72
50-64 Years	52	54	106
>=65 Years	25	35	60
Age continuous			
One participant from Placebo arm was not dosed and hence was not included in the age continuous calculation (N=118).			
Units: years			
arithmetic mean	54.7	57.0	
standard deviation	± 11.19	± 10.96	-
Sex: Female, Male			
Units: Participants			
Female	113	113	226
Male	6	6	12



## End points

### End points reporting groups

Reporting group title	Part A: Linerixibat 40 milligrams (mg)
Reporting group description: Participants were randomized to receive linerixibat 40 mg tablet orally twice a day (BID) in Part A (up to Week 24)	
Reporting group title	Part A: Placebo
Reporting group description: Participants were randomized to receive Placebo orally twice a day (BID) in Part A (up to Week 24).	
Reporting group title	Part B: Placebo in Part A and Part B
Reporting group description: Participants who were randomized to receive Placebo (up to Week 24) orally twice a day (BID) in Part A, continued to receive Placebo (from Week 24 to Week 32) orally twice a day (BID) in Part B.	
Reporting group title	Part B: Placebo in Part A and Linerixibat 40 mg in Part B
Reporting group description: Participants who were randomized to receive Placebo (up to Week 24) orally twice a day (BID) in Part A, switched to receive linerixibat 40 mg tablet orally twice a day (BID) (from Week 24 to Week 32) in Part B.	
Reporting group title	Part B: Linerixibat 40 mg in Part A and Placebo in Part B
Reporting group description: Participants who were randomized to receive linerixibat 40 mg tablet orally BID (up to Week 24) in Part A, switched to receive Placebo (from Week 24 to Week 32) orally twice a day (BID) in Part B.	
Reporting group title	Part B: Linerixibat 40 mg in Part A and Part B
Reporting group description: Participants who were randomized to receive linerixibat 40 mg tablet orally twice a day (BID) (up to Week 24) in Part A, continued to receive linerixibat 40 mg twice a day (BID) (from Week 24 to Week 32) in Part B.	

### Primary: Part A: Mean Change from Baseline in Monthly Itch Scores over 24 weeks using Numerical Rating Scale (NRS)

End point title	Part A: Mean Change from Baseline in Monthly Itch Scores over 24 weeks using Numerical Rating Scale (NRS)
End point description: Itch Scores were assessed using a NRS twice daily, ranging from 0 to 10, where 0 represents no itching and 10 the worst imaginable itching. The worst daily itch score was defined as the worst of the two scores recorded daily. The weekly itch score was defined as the average of the worst daily itch scores in one week. The monthly itch score was defined as the worst weekly itch score for the month (4 weeks). Higher monthly itch scores indicate worse itching. Baseline is the worst weekly itch score in the 28 days prior to randomization (Day 1). Change from Baseline is defined as the post dose value minus baseline value. Least-squares (LS) means and the corresponding 95% confidence intervals are reported by taking average of LS means of change from baseline in monthly itch scores obtained over 24 weeks using equal weighting for all time points. Analyzed using Mixed Model Repeated Measures (MMRM) method. The analysis was performed on the ITT set that included all randomized participants.	
End point type	Primary
End point timeframe: Baseline and up to week 24	

<b>End point values</b>	Part A: Linerixibat 40 milligrams (mg)	Part A: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	118		
Units: Scores on a scale				
least squares mean (confidence interval 95%)	-2.86 (-3.23 to -2.50)	-2.15 (-2.51 to -1.78)		

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Statistical analysis description:	
The mixed model repeated measures analysis includes Treatment Group, Visit, Visit*Treatment Group interaction, Baseline PBC-40 domain scores, Visit*Baseline PBC-40 domain scores interaction, Baseline Concomitant Itch Medication.	
Comparison groups	Part A: Placebo v Part A: Linerixibat 40 milligrams (mg)
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Mixed Model Repeated Measures Analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.15
upper limit	-0.28

## Secondary: Part A: Mean Change from Baseline in Weekly Itch Score using NRS at Week 2

End point title	Part A: Mean Change from Baseline in Weekly Itch Score using NRS at Week 2
End point description:	
Itch Score was assessed using a twice daily NRS, ranging from 0 to 10, where 0 represents no itching and 10 the worst imaginable itching. The worst daily itch score was defined as the worst of the two scores recorded daily. The weekly itch score was defined as the average of the worst daily itch scores in one week. Higher weekly itch scores indicate worse itching. Baseline is the average of the Worst Daily Itch scores in the 7 days prior to randomization (Day 1). Change from Baseline is defined as the Week 2 value minus baseline value. Key secondary endpoints were tested in a step-down/hierarchical approach. Mean Change from Baseline in Weekly Itch Score at Week 2 was the first endpoint tested in the hierarchical analysis. LS mean and the corresponding 95% confidence intervals are reported using Mixed Model Repeated Measures (MMRM) method.	
End point type	Secondary
End point timeframe:	
Baseline and Week 2	

End point values	Part A: Linerixibat 40 milligrams (mg)	Part A: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	116		
Units: Scores on a scale				
least squares mean (confidence interval 95%)	-1.78 (-2.08 to -1.48)	-1.07 (-1.37 to -0.77)		

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
The mixed model repeated measures analysis includes Treatment Group, Week, Week*Treatment Group interaction, Baseline Weekly Itch score (WIS), Visit*Baseline WIS interaction, Baseline Concomitant Itch Medication.	
Comparison groups	Part A: Placebo v Part A: Linerixibat 40 milligrams (mg)
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 <sup>[1]</sup>
Method	Mixed Model Repeated Measures Analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.07
upper limit	-0.34

Notes:

[1] - Adjusted for multiplicity as per Statistical Analysis Plan (SAP)

## Secondary: Part A: Mean Change from Baseline in Monthly Sleep Score as measured by NRS over 24 weeks

End point title	Part A: Mean Change from Baseline in Monthly Sleep Score as measured by NRS over 24 weeks
End point description:	
Sleep Scores were assessed using an NRS scale, ranging from 0 to 10, where 0 represents no sleep interference and 10 is complete sleep interference. The weekly sleep scale is the average of the daily sleep scores for each week. The monthly sleep score was defined as the worst weekly sleep score for the month (4 weeks). Higher monthly sleep scores indicate higher impact on sleep. Baseline is the worst Weekly Sleep Score in the 28 days prior to randomization (Day 1). Change from Baseline is defined as the post dose value minus baseline value. LS means and the corresponding 95% confidence intervals are reported by taking average of LS means of change from baseline in monthly sleep scores obtained over 24 weeks using equal weighting for all time points analyzed using Mixed Model Repeated Measures (MMRM) method. Mean Change from Baseline in Monthly Sleep Score over 24 weeks was the second endpoint tested in the hierarchical analysis.	
End point type	Secondary

End point timeframe:

Baseline and up to week 24

<b>End point values</b>	Part A: Linerixibat 40 milligrams (mg)	Part A: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	118		
Units: Scores on a scale				
least squares mean (confidence interval 95%)	-2.77 (-3.15 to -2.38)	-2.24 (-2.62 to -1.86)		

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
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Statistical analysis description:

The mixed model repeated measures analysis includes Treatment Group, Visit, Visit\*Treatment Group interaction, Baseline PBC-40 domain scores, Visit\*Baseline PBC-40 domain scores interaction, Baseline Concomitant Itch Medication.

Comparison groups	Part A: Placebo v Part A: Linerixibat 40 milligrams (mg)
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.024 <sup>[2]</sup>
Method	Mixed Model Repeated Analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.98
upper limit	-0.07

Notes:

[2] - Adjusted for multiplicity as per Statistical Analysis Plan (SAP)

## Secondary: Part A: Percentage of Responders Defined as Achieving more than or equal to ( $\geq$ ) 2-point Reduction from Baseline in the Monthly Itch Score (MIS) at Week 24

End point title	Part A: Percentage of Responders Defined as Achieving more than or equal to ( $\geq$ ) 2-point Reduction from Baseline in the Monthly Itch Score (MIS) at Week 24
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End point description:

Monthly Itch Score was assessed using an NRS, ranging from 0 to 10, where 0 represents no itching and 10 the worst imaginable itching. The Monthly Itch Score was determined from the worst weekly itch score for the month (4 weeks). Baseline is the worst weekly itch score in the 28 days prior to randomization (Day 1). Responders were defined as participants achieving  $\geq$  2-point reduction (improvement) from baseline in the Monthly Itch Score. Percentage of Responders achieving  $\geq$  2-point Reduction from Baseline in the Monthly Itch Score at Week 24 was the third endpoint tested in the hierarchical analysis. The analysis was performed on the ITT set that included all randomized participants. Participants in the ITT Population were classified according to the treatment as randomized.

Percentage values were rounded to the nearest whole number.

End point type	Secondary
End point timeframe:	
At Week 24	

End point values	Part A: Linerixibat 40 milligrams (mg)	Part A: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	119		
Units: Percentage of participants				
number (not applicable)	68.0	64.0		

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Statistical analysis description:	
Cochran-Mantel-Haenszel (CMH) stratified analysis adjusted for baseline factors: Baseline Itch Severity (Moderate: $\geq 4$ and less than $< 7$ , Severe: $\geq 7$ ); Concomitant cholestatic pruritus treatment regimen (Regimen contains Bile Acid Binding Resin [BABR], Regimen does not contain BABR, No defined treatment). Multiple imputation of missing Monthly itch scores was done before deriving responder definitions. Imputed datasets were analyzed using the CMH method and combined.	
Comparison groups	Part A: Placebo v Part A: Linerixibat 40 milligrams (mg)
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.539 <sup>[3]</sup>
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9
upper limit	17

Notes:

[3] - Adjusted for multiplicity as per Statistical Analysis Plan (SAP)

## Secondary: Part A: Percentage of Responders Defined as Achieving a $\geq 3$ -point Reduction from Baseline in the Monthly Itch Score (MIS) at Week 24

End point title	Part A: Percentage of Responders Defined as Achieving a $\geq 3$ -point Reduction from Baseline in the Monthly Itch Score (MIS) at Week 24
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End point description:

Monthly Itch Score was assessed using an NRS, ranging from 0 to 10, where 0 represents no itching and 10 the worst imaginable itching. The Monthly Itch Score was determined from the worst weekly itch score for the month (4 weeks). Baseline is the worst weekly itch score in the 28 days prior to randomization. Responders were defined as participants achieving  $\geq 3$ -point reduction (improvement) from baseline in the Monthly Itch Score. Percentage of Responders achieving  $\geq 3$ -point Reduction from

Baseline in the Monthly Itch Score at Week 24 was the fourth endpoint to be tested in the hierarchical analysis. The analysis was performed on the ITT set that included all randomized participants. Participants in the ITT Population were classified according to the treatment as randomized. Percentage values were rounded to the nearest whole number.

End point type	Secondary
End point timeframe:	
At Week 24	

End point values	Part A: Linerixibat 40 milligrams (mg)	Part A: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	119		
Units: Percentage of participants				
number (not applicable)	56.0	43.0		

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

Cochran-Mantel-Haenszel (CMH) stratified analysis adjusted for baseline factors: Baseline Itch Severity (Moderate: greater than or equal to  $\geq 4$  and less than  $< 7$ , Severe:  $\geq 7$ ); Concomitant cholestatic pruritus treatment regimen (Regimen contains Bile Acid Binding Resin [BABR], Regimen does not contain BABR, No defined treatment). Multiple imputation of missing MIS was done before deriving responder definitions. Imputed datasets were analyzed using the CMH method and combined.

Comparison groups	Part A: Placebo v Part A: Linerixibat 40 milligrams (mg)
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.043 <sup>[4]</sup>
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	27

Notes:

[4] - Adjusted for multiplicity; two-sided p-values  $< 0.05$  were considered to be nominally significant as per SAP.

## Secondary: Part A: Proportion of Responders Defined as Achieving a $\geq 4$ -point Reduction from Baseline in the Monthly Itch Score (MIS) at Week 24

End point title	Part A: Proportion of Responders Defined as Achieving a $\geq 4$ -point Reduction from Baseline in the Monthly Itch Score (MIS) at Week 24
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End point description:

Monthly Itch Score was assessed using an NRS, ranging from 0 to 10, where 0 represents no itching and 10 the worst imaginable itching. The Monthly Itch Score was determined from the worst weekly itch

score for the month (4 weeks). Baseline is the worst weekly itch score in the 28 days prior to randomization. Responders were defined as participants achieving  $\geq 4$ -point reduction (improvement) from baseline in the Monthly Itch Score. Percentage of Responders achieving  $\geq 4$ -point Reduction from Baseline in the Monthly Itch Score at Week 24 was the fifth endpoint to be tested in the hierarchical analysis. The analysis was performed on the ITT set that included all randomized participants. Participants in the ITT Population were classified according to the treatment as randomized. Percentage values were rounded to the nearest whole number.

End point type	Secondary
End point timeframe:	
At Week 24	

End point values	Part A: Linerixibat 40 milligrams (mg)	Part A: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	119		
Units: Percentage of participants				
number (not applicable)	41.0	29.0		

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

Cochran-Mantel-Haenszel (CMH) stratified analysis adjusted for baseline factors: Baseline Itch Severity (Moderate:  $\geq 4$  and  $< 7$ , Severe:  $\geq 7$ ); Concomitant cholestatic pruritus treatment regimen (Regimen contains BABR, Regimen does not contain BABR, No defined treatment). Multiple imputation of missing Monthly itch scores was done before deriving responder definitions. Imputed datasets were analyzed using the CMH method and combined.

Comparison groups	Part A: Placebo v Part A: Linerixibat 40 milligrams (mg)
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.539 <sup>[5]</sup>
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	24

Notes:

[5] - Adjusted for multiplicity; two-sided p-values  $< 0.05$  were considered to be nominally significant as per SAP.

## Secondary: Part A: Mean Change from Baseline in Primary Biliary Cholangitis-40 (PBC-40) Domain Scores at Week 24

End point title	Part A: Mean Change from Baseline in Primary Biliary Cholangitis-40 (PBC-40) Domain Scores at Week 24
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**End point description:**

PBC40 is disease-specific health-related quality of life(HRQoL) questionnaire. It consists of 40 questions, which are grouped into 6 domains. Each question is scored from 1(least impact) to 5(greatest impact). For all questions, an answer of "Does/Did not apply" was scored 0. All questions within a domain are summed to obtain domain score. Domains were Symptoms(7 questions)-score range 6-35,Itch(3 questions)-score range 0-15,Fatigue(11 questions)-score range 11-55,Cognitive(6 questions)-score range 6-30,Emotional(3 questions)-score range 3-15,Social(10 questions)-score range 8-50. Higher scores for individual domains represent poorer quality of life. Baseline is the last assessment prior to Day 1. Change from Baseline was calculated as Week24 minus Baseline. ITT set included all randomized participants. Number of Participants Analyzed (N) was maximum number of participants analyzed for any domain, while Number analyzed (n) was number of participants included in model for each domain.

End point type	Secondary
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End point timeframe:

Baseline and Week 24

End point values	Part A: Linerixibat 40 milligrams (mg)	Part A: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	100		
Units: Scores on a scale				
least squares mean (confidence interval 95%)				
Cognitive (score range:6-30)(n=99, 95)	-0.71 (-1.60 to 0.18)	-1.47 (-2.36 to -0.58)		
Emotional (score range:3-15)(n=99, 95)	-1.07 (-1.57 to -0.57)	-1.34 (-1.83 to -0.84)		
Fatigue (score range:11-55)(n=100, 95)	-2.94 (-4.63 to -1.26)	-4.54 (-6.21 to -2.86)		
Itch (score range: 0 to 15) (n=100, 95)	-3.47 (-4.08 to -2.86)	-2.89 (-3.50 to -2.28)		
Social (score range:8-50)(n=99, 95)	-2.57 (-3.71 to -1.43)	-2.42 (-3.56 to -1.29)		
Symptoms (score range:6-35)(n=100, 95)	0.54 (-0.18 to 1.25)	0.08 (-0.62 to 0.79)		

**Statistical analyses**

<b>Statistical analysis title</b>	Statistical Analysis 1 (Cognitive)
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**Statistical analysis description:**

The mixed model repeated measures analysis includes Treatment Group, Visit, Visit\*Treatment Group interaction, Baseline PBC-40 domain scores, Visit\*Baseline PBC-40 domain scores interaction, Baseline Concomitant Itch Medication.

Comparison groups	Part A: Placebo v Part A: Linerixibat 40 milligrams (mg)
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.176 <sup>[6]</sup>
Method	Mixed Model Repeated Measures Analysis
Parameter estimate	Mean difference (net)
Point estimate	0.76



Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.34
upper limit	1.86

Notes:

[6] - Not adjusted for multiplicity; two-sided p- values <0.05 were considered to be nominally significant as per SAP.

<b>Statistical analysis title</b>	Statistical Analysis 2 (Emotional)
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Statistical analysis description:

The mixed model repeated measures analysis includes Treatment Group, Visit, Visit\*Treatment Group interaction, Baseline PBC-40 domain scores, Visit\*Baseline PBC-40 domain scores interaction, Baseline Concomitant Itch Medication.

Comparison groups	Part A: Placebo v Part A: Linerixibat 40 milligrams (mg)
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.403 <sup>[7]</sup>
Method	Mixed Model Repeated Measure Analysis
Parameter estimate	Mean difference (net)
Point estimate	0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.36
upper limit	0.89

Notes:

[7] - Not adjusted for multiplicity; two-sided p- values <0.05 were considered to be nominally significant as per SAP.

<b>Statistical analysis title</b>	Statistical Analysis 3 (Fatigue)
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Statistical analysis description:

The mixed model repeated measures analysis includes Treatment Group, Visit, Visit\*Treatment Group interaction, Baseline PBC-40 domain scores, Visit\*Baseline PBC-40 domain scores interaction, Baseline Concomitant Itch Medication.

Comparison groups	Part A: Placebo v Part A: Linerixibat 40 milligrams (mg)
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.132 <sup>[8]</sup>
Method	Mixed Model Repeated Measures
Parameter estimate	Mean difference (net)
Point estimate	1.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.48
upper limit	3.67

Notes:

[8] - Not adjusted for multiplicity; two-sided p- values <0.05 were considered to be nominally significant as per SAP.

<b>Statistical analysis title</b>	Statistical Analysis 4 (Itch)
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**Statistical analysis description:**

The mixed model repeated measures analysis includes Treatment Group, Visit, Visit\*Treatment Group interaction, Baseline PBC-40 domain scores, Visit\*Baseline PBC-40 domain scores interaction, Baseline Concomitant Itch Medication.

Comparison groups	Part A: Placebo v Part A: Linerixibat 40 milligrams (mg)
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.132 <sup>[9]</sup>
Method	Mixed Model Repeated Measures Analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.34
upper limit	0.18

**Notes:**

[9] - Not adjusted for multiplicity; two-sided p- values <0.05 were considered to be nominally significant as per SAP.

<b>Statistical analysis title</b>	Statistical Analysis 5 (Social)
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**Statistical analysis description:**

The mixed model repeated measures analysis includes Treatment Group, Visit, Visit\*Treatment Group interaction, Baseline PBC-40 domain scores, Visit\*Baseline PBC-40 domain scores interaction, Baseline Concomitant Itch Medication.

Comparison groups	Part A: Placebo v Part A: Linerixibat 40 milligrams (mg)
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.836 <sup>[10]</sup>
Method	Mixed Model Repeated Measures Analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.57
upper limit	1.27

**Notes:**

[10] - Not adjusted for multiplicity; two-sided p- values <0.05 were considered to be nominally significant as per SAP.

<b>Statistical analysis title</b>	Statistical Analysis 6 (Symptoms)
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**Statistical analysis description:**

The mixed model repeated measures analysis includes Treatment Group, Visit, Visit\*Treatment Group interaction, Baseline PBC-40 domain scores, Visit\*Baseline PBC-40 domain scores interaction, Baseline Concomitant Itch Medication.

Comparison groups	Part A: Placebo v Part A: Linerixibat 40 milligrams (mg)
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Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.318 <sup>[11]</sup>
Method	Mixed Model Repeated Measure Analysis
Parameter estimate	Mean difference (net)
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.44
upper limit	1.34

Notes:

[11] - Not adjusted for multiplicity; two-sided p- values <0.05 were considered to be nominally significant as per SAP.

## Secondary: Part A: Mean Change from Baseline in Patient's Global Impression of Severity (PGI-S) over 24 weeks

End point title	Part A: Mean Change from Baseline in Patient's Global Impression of Severity (PGI-S) over 24 weeks
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End point description:

The PGI-S is a patient-reported outcome measure used to assess the severity of symptoms from the participant's perspective. The PGI-S asks participant to rate the severity of their itch in the past 7 days on a single item, using a scale ranging from 0 (absent) to 5 (very severe). Higher score indicates higher severity. Baseline is the last assessment prior to the first dose of randomized treatment for Part A (Day 1). Change from Baseline is defined as the post dose value minus baseline value. LS means and the corresponding 95% confidence intervals are reported by taking average of LS means of change from baseline in PGI-S obtained over 24 weeks using equal weighting for all time points, analyzed using MMRM method. The analysis was performed on the ITT set that included all randomized participants. Only participants with data at baseline and at least one post-baseline time point were included.

End point type	Secondary
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End point timeframe:

Baseline up to Week 24

End point values	Part A: Linerixibat 40 milligrams (mg)	Part A: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	111		
Units: Scores on a scale				
least squares mean (confidence interval 95%)	-1.22 (-1.36 to -1.07)	-0.84 (-0.99 to -0.70)		

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

The mixed model repeated measures analysis includes Treatment Group, Visit, Visit\*Treatment Group interaction, Baseline PGI-S score, Visit\*Baseline PGI-S score interaction, Baseline Concomitant Itch Medication.

Comparison groups	Part A: Placebo v Part A: Linerixibat 40 milligrams (mg)
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 <sup>[12]</sup>
Method	Mixed Model Repeated Measure Analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.55
upper limit	-0.2

Notes:

[12] - Not adjusted for multiplicity; two-sided p- values <0.05 were considered to be nominally significant as per SAP.

### Secondary: Part A: Patient's Global Impression of Change (PGI-C) scores over 24 weeks

End point title	Part A: Patient's Global Impression of Change (PGI-C) scores over 24 weeks
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End point description:

Patient's Global Impression of Change (PGI-C) was assessed using a 7-level response scale, ranging from 1 (very much improved) to 7 (very much worse). Higher score indicates higher level of change. LS means and the corresponding 95% confidence intervals are reported by taking average of LS means of PGI-C obtained over 24 weeks using equal weighting for all timepoints, analyzed using Mixed Model Repeated Measures (MMRM) method. The analysis was performed on the ITT set that included all randomized participants. Participants in the ITT Population were classified according to the treatment as randomized. Only participants with data for at least one time point were included.

End point type	Secondary
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End point timeframe:

Week 4 up to 24 weeks

End point values	Part A: Linerixibat 40 milligrams (mg)	Part A: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	116		
Units: Scores on a scale				
least squares mean (confidence interval 95%)	1.97 (1.74 to 2.20)	2.46 (2.23 to 2.69)		

### Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

The mixed model repeated measures analysis includes Treatment Group, Visit, Visit\*Treatment Group interaction, Baseline Concomitant Itch Medication.

Comparison groups	Part A: Placebo v Part A: Linerixibat 40 milligrams (mg)
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Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 <sup>[13]</sup>
Method	Mixed Model Repeated Measure Analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.76
upper limit	-0.21

Notes:

[13] - Not adjusted for multiplicity; two-sided p- values <0.05 were considered to be nominally significant as per SAP.

### Secondary: Part A: Mean Change from Baseline in Alkaline Phosphatase (ALP) at Week 24

End point title	Part A: Mean Change from Baseline in Alkaline Phosphatase (ALP) at Week 24
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End point description:

Blood samples were collected at indicated time points for evaluation of ALP. Change from Baseline in ALP at Week 24 was evaluated. Baseline was established using an average of two sets of laboratory values obtained at least 4 weeks apart within 56 days prior to randomization (Day 1). Change from Baseline was calculated as Week 24 value minus Baseline value. The analysis was performed on the ITT set that included all randomized participants. Participants in the ITT Population were classified according to the treatment as randomized. Only participants with data at baseline and at least one post-baseline time point were included.

End point type	Secondary
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End point timeframe:

Baseline and Week 24

End point values	Part A: Linerixibat 40 milligrams (mg)	Part A: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	107		
Units: International units per Liter (IU/L)				
least squares mean (confidence interval 95%)	10.61 (-8.53 to 29.74)	-8.03 (-26.79 to 10.74)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Part A: Mean change from baseline in Bilirubin at Week 24

End point title	Part A: Mean change from baseline in Bilirubin at Week 24
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**End point description:**

Blood samples were collected at indicated time points for evaluation of Bilirubin. Change from Baseline in total bilirubin at Week 24 was evaluated. Baseline was established using an average of two sets of laboratory values obtained at least 4 weeks apart within 56 days prior to randomization (Day 1). Change from Baseline was calculated as Week 24 value minus Baseline value. The analysis was performed on the ITT set that included all randomized participants. Participants in the ITT Population were classified according to the treatment as randomized. Only participants with data at baseline and at least one post-baseline time point were included.

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End point type	Secondary
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End point timeframe:

Baseline and Week 24

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End point values	Part A: Linerixibat 40 milligrams (mg)	Part A: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	107		
Units: Micromoles per Liter (mmol/L)				
least squares mean (confidence interval 95%)	1.77 (0.84 to 2.71)	-0.31 (-1.24 to 0.62)		

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**Statistical analyses**

No statistical analyses for this end point

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## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

SAEs were collected from the signing of informed consent until last visit (Week 32) or follow up phone call. AEs were collected from start of treatment until last visit (Week 32) or follow up phone call.

Adverse event reporting additional description:

All randomized participants from ITT population (N=238) were included in Part A. One participant in Part A was not included in Safety population (N=237) and 15 participants from ITT Population (N=211) in Part B were not included in Safety population (N=196) as they did not receive study intervention.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	27.1
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### Reporting groups

Reporting group title	Part A: Placebo
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Reporting group description:

Participants were randomized to receive Placebo in Part A (up to Week 24).

Reporting group title	Part A: Linerixibat 40 milligrams (mg)
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Reporting group description:

Participants were randomized to receive Linerixibat 40 mg orally twice a day (BID) in Part A (up to Week 24).

Reporting group title	Part B: Placebo in Part A and Part B
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Reporting group description:

Participants who were randomized to receive Placebo (up to Week 24) in Part A, continued to receive Placebo (from Week 24 to Week 32) in Part B.

Reporting group title	Part B: Placebo in Part A and Linerixibat 40 mg in Part B
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Reporting group description:

Participants who were randomized to receive Placebo (up to Week 24) in Part A, switched to receive Linerixibat 40 mg BID (from Week 24 to Week 32) in Part B.

Reporting group title	Part B: Linerixibat 40 mg in Part A and Placebo in Part B
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Reporting group description:

Participants who were randomized to receive Linerixibat 40 mg BID (up to Week 24) in Part A, switched to receive Placebo (from Week 24 to Week 32) in Part B.

Reporting group title	Part B: Linerixibat 40 mg in Part A and Part B
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Reporting group description:

Participants who were randomized to receive Linerixibat 40 mg BID (up to Week 24) in Part A, continued to receive Linerixibat 40 mg BID (from Week 24 to Week 32) in Part B.

Serious adverse events	Part A: Placebo	Part A: Linerixibat 40 milligrams (mg)	Part B: Placebo in Part A and Part B
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 118 (3.39%)	14 / 119 (11.76%)	0 / 53 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood pressure increased			

subjects affected / exposed	0 / 118 (0.00%)	1 / 119 (0.84%)	0 / 53 (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
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	0 / 118 (0.00%)	1 / 119 (0.84%)	0 / 53 (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
Renal cell carcinoma			
subjects affected / exposed	0 / 118 (0.00%)	0 / 119 (0.00%)	0 / 53 (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
Cardiac disorders			
Sinus arrest			
subjects affected / exposed	1 / 118 (0.85%)	0 / 119 (0.00%)	0 / 53 (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
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 118 (0.00%)	1 / 119 (0.84%)	0 / 53 (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
Cerebrovascular accident			
subjects affected / exposed	0 / 118 (0.00%)	1 / 119 (0.84%)	0 / 53 (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
Dizziness			
subjects affected / exposed	1 / 118 (0.85%)	0 / 119 (0.00%)	0 / 53 (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	1 / 118 (0.85%)	0 / 119 (0.00%)	0 / 53 (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 / 118 (0.00%)	1 / 119 (0.84%)	0 / 53 (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
Haemorrhagic disorder			
subjects affected / exposed	0 / 118 (0.00%)	1 / 119 (0.84%)	0 / 53 (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
Thrombocytosis			
subjects affected / exposed	0 / 118 (0.00%)	0 / 119 (0.00%)	0 / 53 (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			
Ascites			
subjects affected / exposed	0 / 118 (0.00%)	1 / 119 (0.84%)	0 / 53 (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
Gastric haemorrhage			
subjects affected / exposed	0 / 118 (0.00%)	1 / 119 (0.84%)	0 / 53 (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
Gastric mucosal lesion			
subjects affected / exposed	0 / 118 (0.00%)	1 / 119 (0.84%)	0 / 53 (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
Reproductive system and breast disorders			
Intermenstrual bleeding			
subjects affected / exposed	1 / 118 (0.85%)	0 / 119 (0.00%)	0 / 53 (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			
Cholecystitis			

subjects affected / exposed	0 / 118 (0.00%)	1 / 119 (0.84%)	0 / 53 (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
<b>Musculoskeletal and connective tissue disorders</b>			
Arthritis			
subjects affected / exposed	0 / 118 (0.00%)	1 / 119 (0.84%)	0 / 53 (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
Back pain			
subjects affected / exposed	0 / 118 (0.00%)	1 / 119 (0.84%)	0 / 53 (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
Intervertebral disc protrusion			
subjects affected / exposed	0 / 118 (0.00%)	1 / 119 (0.84%)	0 / 53 (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
<b>Infections and infestations</b>			
Clostridium difficile colitis			
subjects affected / exposed	0 / 118 (0.00%)	1 / 119 (0.84%)	0 / 53 (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
Diverticulitis			
subjects affected / exposed	1 / 118 (0.85%)	0 / 119 (0.00%)	0 / 53 (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
<b>Metabolism and nutrition disorders</b>			
Diabetes mellitus			
subjects affected / exposed	1 / 118 (0.85%)	0 / 119 (0.00%)	0 / 53 (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
<b>Serious adverse events</b>			
	Part B: Placebo in Part A and Linerixibat 40 mg in Part B	Part B: Linerixibat 40 mg in Part A and Placebo in Part B	Part B: Linerixibat 40 mg in Part A and Part B
Total subjects affected by serious adverse events			

subjects affected / exposed	0 / 52 (0.00%)	2 / 46 (4.35%)	0 / 45 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 52 (0.00%)	0 / 46 (0.00%)	0 / 45 (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
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	0 / 52 (0.00%)	0 / 46 (0.00%)	0 / 45 (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
Renal cell carcinoma			
subjects affected / exposed	0 / 52 (0.00%)	1 / 46 (2.17%)	0 / 45 (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
Cardiac disorders			
Sinus arrest			
subjects affected / exposed	0 / 52 (0.00%)	0 / 46 (0.00%)	0 / 45 (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
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 52 (0.00%)	0 / 46 (0.00%)	0 / 45 (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
Cerebrovascular accident			
subjects affected / exposed	0 / 52 (0.00%)	0 / 46 (0.00%)	0 / 45 (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
Dizziness			
subjects affected / exposed	0 / 52 (0.00%)	0 / 46 (0.00%)	0 / 45 (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

Syncope			
subjects affected / exposed	0 / 52 (0.00%)	0 / 46 (0.00%)	0 / 45 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 46 (0.00%)	0 / 45 (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
Haemorrhagic disorder			
subjects affected / exposed	0 / 52 (0.00%)	0 / 46 (0.00%)	0 / 45 (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
Thrombocytosis			
subjects affected / exposed	0 / 52 (0.00%)	1 / 46 (2.17%)	0 / 45 (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
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	0 / 52 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	0 / 52 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric mucosal lesion			
subjects affected / exposed	0 / 52 (0.00%)	0 / 46 (0.00%)	0 / 45 (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
Reproductive system and breast disorders			
Intermenstrual bleeding			

subjects affected / exposed	0 / 52 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 52 (0.00%)	0 / 46 (0.00%)	0 / 45 (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
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 52 (0.00%)	0 / 46 (0.00%)	0 / 45 (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
Back pain			
subjects affected / exposed	0 / 52 (0.00%)	0 / 46 (0.00%)	0 / 45 (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
Intervertebral disc protrusion			
subjects affected / exposed	0 / 52 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	0 / 52 (0.00%)	0 / 46 (0.00%)	0 / 45 (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
Diverticulitis			
subjects affected / exposed	0 / 52 (0.00%)	0 / 46 (0.00%)	0 / 45 (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			
Diabetes mellitus			

subjects affected / exposed	0 / 52 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

<b>Non-serious adverse events</b>	Part A: Placebo	Part A: Linerixibat 40 milligrams (mg)	Part B: Placebo in Part A and Part B
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 118 (45.76%)	96 / 119 (80.67%)	5 / 53 (9.43%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 118 (3.39%)	11 / 119 (9.24%)	0 / 53 (0.00%)
occurrences (all)	4	12	0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 118 (0.85%)	10 / 119 (8.40%)	0 / 53 (0.00%)
occurrences (all)	1	11	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 118 (2.54%)	7 / 119 (5.88%)	0 / 53 (0.00%)
occurrences (all)	4	7	0
Headache			
subjects affected / exposed	4 / 118 (3.39%)	10 / 119 (8.40%)	0 / 53 (0.00%)
occurrences (all)	5	10	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 118 (5.93%)	2 / 119 (1.68%)	0 / 53 (0.00%)
occurrences (all)	8	2	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 118 (0.00%)	0 / 119 (0.00%)	2 / 53 (3.77%)
occurrences (all)	0	0	2
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	6 / 118 (5.08%)	8 / 119 (6.72%)	0 / 53 (0.00%)
occurrences (all)	6	10	0
Abdominal pain			

subjects affected / exposed occurrences (all)	4 / 118 (3.39%) 4	22 / 119 (18.49%) 27	0 / 53 (0.00%) 0
Abdominal pain upper subjects affected / exposed occurrences (all)	5 / 118 (4.24%) 6	8 / 119 (6.72%) 14	0 / 53 (0.00%) 0
Constipation subjects affected / exposed occurrences (all)	11 / 118 (9.32%) 11	9 / 119 (7.56%) 9	0 / 53 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	21 / 118 (17.80%) 28	72 / 119 (60.50%) 112	3 / 53 (5.66%) 3
Dyspepsia subjects affected / exposed occurrences (all)	1 / 118 (0.85%) 1	9 / 119 (7.56%) 9	0 / 53 (0.00%) 0
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	5 / 118 (4.24%) 9	8 / 119 (6.72%) 13	0 / 53 (0.00%) 0
Nausea subjects affected / exposed occurrences (all)	11 / 118 (9.32%) 13	12 / 119 (10.08%) 17	0 / 53 (0.00%) 0
Skin and subcutaneous tissue disorders Cholestatic pruritus subjects affected / exposed occurrences (all)	0 / 118 (0.00%) 0	0 / 119 (0.00%) 0	0 / 53 (0.00%) 0
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	6 / 118 (5.08%) 9	7 / 119 (5.88%) 8	0 / 53 (0.00%) 0
Infections and infestations COVID-19 subjects affected / exposed occurrences (all)	3 / 118 (2.54%) 3	8 / 119 (6.72%) 9	0 / 53 (0.00%) 0

<b>Non-serious adverse events</b>	Part B: Placebo in Part A and Linerixibat 40 mg in Part B	Part B: Linerixibat 40 mg in Part A and Placebo in Part B	Part B: Linerixibat 40 mg in Part A and Part B
Total subjects affected by non-serious adverse events			

subjects affected / exposed	16 / 52 (30.77%)	3 / 46 (6.52%)	7 / 45 (15.56%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 52 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 52 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 52 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	0 / 52 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 52 (5.77%)	0 / 46 (0.00%)	1 / 45 (2.22%)
occurrences (all)	3	0	1
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 52 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			
subjects affected / exposed	0 / 52 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 52 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 52 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			



subjects affected / exposed	14 / 52 (26.92%)	0 / 46 (0.00%)	6 / 45 (13.33%)
occurrences (all)	18	0	12
Dyspepsia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 52 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 52 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Cholestatic pruritus			
subjects affected / exposed	0 / 52 (0.00%)	3 / 46 (6.52%)	0 / 45 (0.00%)
occurrences (all)	0	3	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 52 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0

**More information**

**Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 January 2021	Original Protocol
01 March 2021	Amendment 1
12 July 2021	Amendment 2
02 September 2021	Amendment 3
20 November 2023	Amendment 4

Notes:

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**Interruptions (globally)**

Were there any global interruptions to the trial? No

**Limitations and caveats**

None reported