Clinical trial results:
Randomized, Double-blind, Placebo-Controlled Phase 2 Study to Evaluate the Efficacy and Safety of Maralixibat in the Treatment of Subjects with Biliary Atresia after Hepatoportoenterostomy

Summary

EudraCT number	2020-000974-22
Trial protocol	DE FR PL GB IT
Global end of trial date	07 February 2024

Results information

Result version number	v2 (current)
This version publication date	24 November 2024
First version publication date	23 August 2024
Version creation reason	• Correction of full data set AE number correction

Trial information

Trial identification

Sponsor protocol code	MRX-701

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04524390
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Mirum Pharmaceuticals Inc.
Sponsor organisation address	989 E Hillsdale Blvd. Suite 300 , Foster City, United States, 94404
Public contact	Chief Development Officer, Mirum Pharmaceuticals, Inc., 1 6506674085, medinfo@mirumpharma.com
Scientific contact	Chief Development Officer, Mirum Pharmaceuticals, Inc., 1 6506674085, medinfo@mirumpharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001475-PIP04-20
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 February 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 February 2024
Global end of trial reached?	Yes
Global end of trial date	07 February 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of maralixibat on biliary drainage after hepatoportoenterostomy (HPE) in participants with BA.

Protection of trial subjects:

All study participants (caregivers as applicable) were required to read and sign an Informed Consent Form (ICF). Participants were re-consented to the most current version of the ICF(s) during their participation in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 October 2020
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	Singapore: 1
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	United States: 5
Country: Number of subjects enrolled	Viet Nam: 17
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	China: 36
Worldwide total number of subjects	75
EEA total number of subjects	3

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)	75

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

Subject disposition

Recruitment

Recruitment details:

A total of 75 participants were enrolled at 19 sites across 8 countries (China, Germany, Poland, Singapore, Taiwan, United Kingdom, United States, and Vietnam).

Pre-assignment

Screening details:

The screening period starts when informed consent (by the legally authorized representative) is signed. The duration of the screening period is up to 3 weeks, during which all procedures listed for the screening visit in the schedule of assessment must be completed. A total of 77 patients were screened.

Period 1

Period 1 title	Double Blind
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Participants who meet all eligibility criteria were randomized 1:1 at the baseline visit to receive maralixibat or placebo.

Arms

Are arms mutually exclusive?	Yes
Arm title	Maralixibat

Arm description:

The double-blind period comprised of 4-8 weeks of dose escalation followed by 18 - 22 weeks of stable dosing treatment. After 20 participants had completed dose escalation, a Data Monitoring Committee (DMC) review took place to analyze the potential to simplify dose escalation to a 2-step regimen.

Arm type	Experimental
Investigational medicinal product name	Maralixibat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution in bottle
Routes of administration	Oral use

Dosage and administration details:

Dose Escalation (4-8 Weeks)
For participants ≥1 month of age assigned to maralixibat in the double-blind period, the dose-escalation treatment will consist of the following steps:
• Dose level 1: 150 µg/kg maralixibat BID for 1–2 weeks
• Dose level 2: 300 µg/kg maralixibat BID for 1–2 weeks
• Dose level 3: 450 µg/kg maralixibat BID for 1–2 weeks
• Dose level 4: 600 µg/kg maralixibat BID (or highest tolerated) for the remaining duration of the dosing period

Following DMC recommendation the below simplified dose escalation was implemented:
• Dose level 1: 300 µg/kg maralixibat BID for 1–2 weeks
• Dose level 2: 600 µg/kg maralixibat BID (or highest tolerated) for the remaining duration of the dosing period

For participants <1 month of age, doses of maralixibat 75 µg/kg QD should be given.

Stable Dosing (18-22)
During the stable dosing treatment, participants will continue treatment with the highest tolerated dose from the dose escalation period.

Arm title	Placebo

Arm description:

The double-blind period comprised of 4-8 weeks of dose escalation followed by 18 - 22 weeks of stable dosing treatment. After 20 participants had completed dose escalation, a Data Monitoring Committee (DMC) review took place to analyze the potential to simplify dose escalation to a 2-step regimen.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution in bottle
Routes of administration	Oral use

Dosage and administration details:

Dose Escalation (4-8 weeks)
For participants ≥1 month of age assigned to maralixibat in the double-blind period, the dose-escalation period (4–8 weeks) will consist of the following steps:
• Dose level 1: 150 µg/kg Placebo BID for 1–2 weeks
• Dose level 2: 300 µg/kg Placebo BID for 1–2 weeks
• Dose level 3: 450 µg/kg Placebo BID for 1–2 weeks
• Dose level 4: 600 µg/kg Placebo BID (or highest tolerated) for the remaining duration of the dosing period

Following DMC recommendation the below simplified dose escalation was implemented:
• Dose level 1: 300 µg/kg Placebo BID for 1–2 weeks
• Dose level 2: 600 µg/kg Placebo BID (or highest tolerated) for the remaining duration of the dosing period less

For participants <1 month of age, doses of Placebo 75 µg/kg QD should be given.

Stable Dosing (18-22)
During the stable dosing treatment, participants will continue treatment with the highest tolerated dose from the dose escalation period.

Number of subjects in period 1	Maralixibat	Placebo
Started	40	35
Completed	28	24
Not completed	12	11
Consent withdrawn by subject	2	1
Adverse event, non-fatal	5	3
Liver Transplant	5	6
Disease Progression	-	1

Period 2

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

Blinding implementation details:

N/A

Arms

Arm title	Open Label Extension

Arm description:

The Open-Label period comprised of 4-8 weeks of dose escalation followed by 70 - 74 weeks of stable dosing treatment. After 20 participants had completed dose escalation during the Double-Blind Period, a Data Monitoring Committee (DMC) review took place to analyze the potential to simplify dose escalation to a 2-step regimen. During the OLE, all participants, regardless of treatment assignment in the double-blind period, received maralixibat.

Arm type	Experimental
Investigational medicinal product name	Maralixibat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution in bottle
Routes of administration	Oral use

Dosage and administration details:

Dose Escalation (4-8 Weeks)
For participants ≥1 month of age assigned to maralixibat in the double-blind period, the dose-escalation treatment will consist of the following steps:
• Dose level 1: 150 µg/kg maralixibat BID for 1–2 weeks
• Dose level 2: 300 µg/kg maralixibat BID for 1–2 weeks
• Dose level 3: 450 µg/kg maralixibat BID for 1–2 weeks
• Dose level 4: 600 µg/kg maralixibat BID (or highest tolerated) for the remaining duration of the dosing period

Following DMC recommendation the below simplified dose escalation was implemented:
• Dose level 1: 300 µg/kg maralixibat BID for 1–2 weeks
• Dose level 2: 600 µg/kg maralixibat BID (or highest tolerated) for the remaining duration of the dosing period

Stable Dosing (70-74 weeks)
During the stable dosing treatment, participants will continue treatment with the highest tolerated dose from the dose escalation period.

Number of subjects in period 2	Open Label Extension
Started	52
Completed	1
Not completed	51
Drug Interruption Criteria	1
Adverse event, non-fatal	3
Study Termination by sponsor	45
Liver Transplant	1
Disease Progression	1

Baseline characteristics

Reporting groups

Reporting group title	Double Blind

Reporting group description: -

Reporting group values	Double Blind	Total	
Number of subjects	75	75	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	75	75	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: days			
median	76.1		
standard deviation	± 17.63	-	
Gender categorical Units: Subjects			
Female	36	36	
Male	39	39	

Subject analysis sets

Subject analysis set title	All participants
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomized participants. Additional subgroups of the ITT population will be specified based on the presence/absence of post-baseline efficacy assessments for particular efficacy endpoints

Reporting group values	All participants		
Number of subjects	75		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	75		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		

Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: days			
median	76.1		
standard deviation	± 17.63		
Gender categorical			
Units: Subjects			
Female	36		
Male	39		

End points

End points reporting groups

Reporting group title	Maralixibat

Reporting group description:

The double-blind period comprised of 4-8 weeks of dose escalation followed by 18 - 22 weeks of stable dosing treatment. After 20 participants had completed dose escalation, a Data Monitoring Committee (DMC) review took place to analyze the potential to simplify dose escalation to a 2-step regimen.

Reporting group title	Placebo

Reporting group description:

The double-blind period comprised of 4-8 weeks of dose escalation followed by 18 - 22 weeks of stable dosing treatment. After 20 participants had completed dose escalation, a Data Monitoring Committee (DMC) review took place to analyze the potential to simplify dose escalation to a 2-step regimen.

Reporting group title	Open Label Extension

Reporting group description:

The Open-Label period comprised of 4-8 weeks of dose escalation followed by 70 - 74 weeks of stable dosing treatment. After 20 participants had completed dose escalation during the Double-Blind Period, a Data Monitoring Committee (DMC) review took place to analyze the potential to simplify dose escalation to a 2-step regimen. During the OLE, all participants, regardless of treatment assignment in the double-blind period, received maralixibat.

Subject analysis set title	All participants
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomized participants. Additional subgroups of the ITT population will be specified based on the presence/absence of post-baseline efficacy assessments for particular efficacy endpoints

Primary: Mean change in Total Serum Bilirubin

End point title	Mean change in Total Serum Bilirubin

End point description:

End point type	Primary

End point timeframe:

Baseline through week 26

End point values	Maralixibat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	35		
Units: mg/dL				
least squares mean (standard error)	-3.5 (± 0.853)	-3.11 (± 0.947)		

Statistical analyses

Statistical analysis title	Mean change in Total Serum Bilirubin
Comparison groups	Maralixibat v Placebo

Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7419
Method	MMRM
Parameter estimate	Least-Square mean
Point estimate	-0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.76
upper limit	1.97
Variability estimate	Standard error of the mean
Dispersion value	1.182

Secondary: Mean change in total Serum Bile Acids

End point title	Mean change in total Serum Bile Acids
End point description:	
End point type	Secondary
End point timeframe:	
Baseline through week 26	

End point values	Maralixibat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	35		
Units: umol/L				
least squares mean (standard error)	-51.19 (± 25.436)	-5.29 (± 28.440)		

Statistical analyses

Statistical analysis title	Mean change in total Serum Bile Acids
Comparison groups	Maralixibat v Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2002
Method	MMRM
Parameter estimate	Least-Square mean
Point estimate	-45.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-116.86
upper limit	25.05
Variability estimate	Standard error of the mean
Dispersion value	35.398

Secondary: Proportion of participants with mean TSB levels <2 mg/dL

End point title	Proportion of participants with mean TSB levels <2 mg/dL
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to Week 26	

End point values	Maralixibat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	35		
Units: Number of participants	24	20		

Statistical analyses

Statistical analysis title	MRX vs PCB
Comparison groups	Maralixibat v Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8412
Method	Barnard's exact test

Secondary: Proportion of participants observed to have a liver-related clinical event

End point title	Proportion of participants observed to have a liver-related clinical event
End point description:	
End point type	Secondary
End point timeframe:	
Baseline Through Week 26	

End point values	Maralixibat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	35		
Units: Number of Participants	8	7		

Statistical analyses

Statistical analysis title	MRX vs PCB
Comparison groups	Placebo v Maralixibat
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.9999
Method	Barnard's exact test

Secondary: Proportion of participants undergoing liver transplantation or death

End point title	Proportion of participants undergoing liver transplantation or death

End point description:

End point type	Secondary

End point timeframe:

Baseline Through Week 26

End point values	Maralixibat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	35		
Units: Number of Participants	5	3		

Statistical analyses

Statistical analysis title	MRX vs PCB
Comparison groups	Maralixibat v Placebo

Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6658
Method	Barnard's exact test

Secondary: Proportion of participants observed to develop clinically evident portal hypertension

End point title	Proportion of participants observed to develop clinically evident portal hypertension

End point description:

End point type	Secondary

End point timeframe:

Baseline through Week 26

End point values	Maralixibat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	35		
Units: Number of Participants	3	4		

Statistical analyses

Statistical analysis title	MRX vs PCB
Comparison groups	Maralixibat v Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6236
Method	Barnard's exact test

Secondary: Proportion of participants with mean TSB levels ≤1.2 mg/dL

End point title	Proportion of participants with mean TSB levels ≤1.2 mg/dL

End point description:

End point type	Secondary

End point timeframe:

Baseline through Week 26

End point values	Maralixibat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	35		
Units: Number of Participants	23	18		

Statistical analyses

Statistical analysis title	MRX vs PCB
Comparison groups	Maralixibat v Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6658
Method	Barnard's exact test

Secondary: Proportion of participants with mean sBA levels ≤40 mmol/L

End point title	Proportion of participants with mean sBA levels ≤40 mmol/L

End point description:

End point type	Secondary

End point timeframe:

Baseline through Week 26

End point values	Maralixibat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	35		
Units: Number of participants	10	7		

Statistical analyses

Statistical analysis title	MRX vs PCB
Comparison groups	Maralixibat v Placebo

Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6659
Method	Barnard's exact test

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline to EOT	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups	
Reporting group title	Safety Population OLE Maralixibat
Reporting group description:	
All participants who receive at least 1 dose of study medication during the Open-Label Maralixibat Period.	
Reporting group title	Safety Population Double Blinded Maralixibat
Reporting group description:	
All participants who receive at least 1 dose of study medication during the double-blinded Maralixibat Period.	
Reporting group title	Safety Population Double Blinded Placebo
Reporting group description:	
All participants who receive at least 1 dose of study medication during the double-blinded Placebo Period.	

Serious adverse events	Safety Population OLE Maralixibat	Safety Population Double Blinded Maralixibat	Safety Population Double Blinded Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 52 (40.38%)	26 / 40 (65.00%)	25 / 35 (71.43%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 52 (0.00%)	0 / 40 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	1 / 52 (1.92%)	2 / 40 (5.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental exposure to product by child			

subjects affected / exposed	1 / 52 (1.92%)	0 / 40 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural complication			
subjects affected / exposed	1 / 52 (1.92%)	0 / 40 (0.00%)	0 / 35 (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			
Coagulopathy			
subjects affected / exposed	0 / 52 (0.00%)	1 / 40 (2.50%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 52 (1.92%)	1 / 40 (2.50%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 52 (1.92%)	0 / 40 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 52 (1.92%)	0 / 40 (0.00%)	0 / 35 (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
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 52 (0.00%)	2 / 40 (5.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faeces discoloured			

subjects affected / exposed	0 / 52 (0.00%)	1 / 40 (2.50%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 52 (0.00%)	1 / 40 (2.50%)	0 / 35 (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
Ileus			
subjects affected / exposed	1 / 52 (1.92%)	0 / 40 (0.00%)	0 / 35 (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
Mouth ulceration			
subjects affected / exposed	0 / 52 (0.00%)	0 / 40 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 52 (0.00%)	1 / 40 (2.50%)	0 / 35 (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
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	8 / 52 (15.38%)	17 / 40 (42.50%)	18 / 35 (51.43%)
occurrences causally related to treatment / all	0 / 10	1 / 28	0 / 27
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis acute			
subjects affected / exposed	0 / 52 (0.00%)	0 / 40 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			
subjects affected / exposed	1 / 52 (1.92%)	0 / 40 (0.00%)	0 / 35 (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
Hyperbilirubinaemia			

subjects affected / exposed	0 / 52 (0.00%)	1 / 40 (2.50%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	0 / 52 (0.00%)	1 / 40 (2.50%)	0 / 35 (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
Liver injury			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 52 (1.92%)	0 / 40 (0.00%)	0 / 35 (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
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	1 / 52 (1.92%)	0 / 40 (0.00%)	0 / 35 (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			
Adenovirus infection			
subjects affected / exposed	2 / 52 (3.85%)	0 / 40 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiolitis			
subjects affected / exposed	1 / 52 (1.92%)	2 / 40 (5.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	0 / 52 (0.00%)	1 / 40 (2.50%)	3 / 35 (8.57%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus infection			
subjects affected / exposed	0 / 52 (0.00%)	1 / 40 (2.50%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastroenteritis			
subjects affected / exposed	2 / 52 (3.85%)	0 / 40 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	1 / 52 (1.92%)	0 / 40 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media			
subjects affected / exposed	1 / 52 (1.92%)	0 / 40 (0.00%)	0 / 35 (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
Parainfluenzae virus infection			
subjects affected / exposed	0 / 52 (0.00%)	2 / 40 (5.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pertussis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 40 (0.00%)	0 / 35 (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
Pharyngitis			
subjects affected / exposed	0 / 52 (0.00%)	0 / 40 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 52 (3.85%)	8 / 40 (20.00%)	4 / 35 (11.43%)
occurrences causally related to treatment / all	0 / 2	0 / 13	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	0 / 52 (0.00%)	0 / 40 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus infection			

subjects affected / exposed	0 / 52 (0.00%)	1 / 40 (2.50%)	0 / 35 (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
Respiratory tract infection			
subjects affected / exposed	0 / 52 (0.00%)	0 / 40 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhinovirus infection			
subjects affected / exposed	0 / 52 (0.00%)	1 / 40 (2.50%)	0 / 35 (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
Rotavirus infection			
subjects affected / exposed	1 / 52 (1.92%)	1 / 40 (2.50%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 52 (0.00%)	0 / 40 (0.00%)	2 / 35 (5.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 52 (1.92%)	0 / 40 (0.00%)	0 / 35 (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
Urinary tract infection			
subjects affected / exposed	1 / 52 (1.92%)	0 / 40 (0.00%)	0 / 35 (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
Viral infection			
subjects affected / exposed	1 / 52 (1.92%)	0 / 40 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperinsulinism			

subjects affected / exposed	0 / 52 (0.00%)	0 / 40 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Safety Population OLE Maralixibat	Safety Population Double Blinded Maralixibat	Safety Population Double Blinded Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 52 (90.38%)	38 / 40 (95.00%)	33 / 35 (94.29%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 52 (7.69%)	5 / 40 (12.50%)	5 / 35 (14.29%)
occurrences (all)	6	5	5
Blood bilirubin increased			
subjects affected / exposed	1 / 52 (1.92%)	1 / 40 (2.50%)	2 / 35 (5.71%)
occurrences (all)	1	3	2
Hepatic enzyme increased			
subjects affected / exposed	1 / 52 (1.92%)	3 / 40 (7.50%)	0 / 35 (0.00%)
occurrences (all)	1	3	0
Spleen palpable			
subjects affected / exposed	1 / 52 (1.92%)	0 / 40 (0.00%)	2 / 35 (5.71%)
occurrences (all)	1	0	2
Vitamin A decreased			
subjects affected / exposed	1 / 52 (1.92%)	0 / 40 (0.00%)	2 / 35 (5.71%)
occurrences (all)	1	0	2
Injury, poisoning and procedural complications			
Scratch			
subjects affected / exposed	0 / 52 (0.00%)	0 / 40 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 52 (5.77%)	1 / 40 (2.50%)	3 / 35 (8.57%)
occurrences (all)	3	1	5
Coagulopathy			

subjects affected / exposed	2 / 52 (3.85%)	2 / 40 (5.00%)	3 / 35 (8.57%)
occurrences (all)	3	3	4
Splenomegaly			
subjects affected / exposed	1 / 52 (1.92%)	2 / 40 (5.00%)	1 / 35 (2.86%)
occurrences (all)	1	2	1
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	12 / 52 (23.08%)	14 / 40 (35.00%)	8 / 35 (22.86%)
occurrences (all)	18	19	8
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	13 / 52 (25.00%)	13 / 40 (32.50%)	8 / 35 (22.86%)
occurrences (all)	16	19	8
Vomiting			
subjects affected / exposed	2 / 52 (3.85%)	4 / 40 (10.00%)	6 / 35 (17.14%)
occurrences (all)	2	4	8
Dyspepsia			
subjects affected / exposed	0 / 52 (0.00%)	2 / 40 (5.00%)	0 / 35 (0.00%)
occurrences (all)	0	2	0
Haematochezia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 40 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	4
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	3 / 52 (5.77%)	6 / 40 (15.00%)	6 / 35 (17.14%)
occurrences (all)	3	8	6
Hepatomegaly			
subjects affected / exposed	0 / 52 (0.00%)	1 / 40 (2.50%)	2 / 35 (5.71%)
occurrences (all)	0	1	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 52 (15.38%)	8 / 40 (20.00%)	5 / 35 (14.29%)
occurrences (all)	9	9	6
Skin and subcutaneous tissue disorders			
Dermatitis diaper			

subjects affected / exposed	5 / 52 (9.62%)	3 / 40 (7.50%)	0 / 35 (0.00%)
occurrences (all)	8	6	0
Eczema			
subjects affected / exposed	1 / 52 (1.92%)	6 / 40 (15.00%)	4 / 35 (11.43%)
occurrences (all)	1	9	4
Rash			
subjects affected / exposed	2 / 52 (3.85%)	3 / 40 (7.50%)	3 / 35 (8.57%)
occurrences (all)	2	3	3
Urticaria			
subjects affected / exposed	3 / 52 (5.77%)	1 / 40 (2.50%)	0 / 35 (0.00%)
occurrences (all)	4	1	0
Pruritus			
subjects affected / exposed	0 / 52 (0.00%)	0 / 40 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 52 (7.69%)	3 / 40 (7.50%)	3 / 35 (8.57%)
occurrences (all)	5	3	3
COVID-19			
subjects affected / exposed	2 / 52 (3.85%)	3 / 40 (7.50%)	5 / 35 (14.29%)
occurrences (all)	2	3	5
Nasopharyngitis			
subjects affected / exposed	3 / 52 (5.77%)	1 / 40 (2.50%)	1 / 35 (2.86%)
occurrences (all)	7	1	1
Otitis media			
subjects affected / exposed	3 / 52 (5.77%)	0 / 40 (0.00%)	1 / 35 (2.86%)
occurrences (all)	3	0	2
Pharyngitis			
subjects affected / exposed	1 / 52 (1.92%)	2 / 40 (5.00%)	1 / 35 (2.86%)
occurrences (all)	1	2	1
Pneumonia			
subjects affected / exposed	5 / 52 (9.62%)	6 / 40 (15.00%)	5 / 35 (14.29%)
occurrences (all)	6	8	8
Respiratory tract infection			
subjects affected / exposed	2 / 52 (3.85%)	1 / 40 (2.50%)	2 / 35 (5.71%)
occurrences (all)	2	1	2

Upper respiratory tract infection			
subjects affected / exposed	12 / 52 (23.08%)	7 / 40 (17.50%)	3 / 35 (8.57%)
occurrences (all)	23	8	5
Viral upper respiratory tract infection			
subjects affected / exposed	4 / 52 (7.69%)	1 / 40 (2.50%)	4 / 35 (11.43%)
occurrences (all)	6	1	5
Cytomegalovirus infection			
subjects affected / exposed	0 / 52 (0.00%)	2 / 40 (5.00%)	1 / 35 (2.86%)
occurrences (all)	0	2	1
Gastroenteritis			
subjects affected / exposed	3 / 52 (5.77%)	0 / 40 (0.00%)	0 / 35 (0.00%)
occurrences (all)	3	0	0
Influenza			
subjects affected / exposed	3 / 52 (5.77%)	0 / 40 (0.00%)	0 / 35 (0.00%)
occurrences (all)	3	0	0
Parainfluenzae virus infection			
subjects affected / exposed	0 / 52 (0.00%)	2 / 40 (5.00%)	0 / 35 (0.00%)
occurrences (all)	0	2	0
Metabolism and nutrition disorders			
Vitamin A deficiency			
subjects affected / exposed	3 / 52 (5.77%)	3 / 40 (7.50%)	7 / 35 (20.00%)
occurrences (all)	3	3	7
Vitamin D deficiency			
subjects affected / exposed	8 / 52 (15.38%)	7 / 40 (17.50%)	9 / 35 (25.71%)
occurrences (all)	8	7	9
Vitamin E deficiency			
subjects affected / exposed	4 / 52 (7.69%)	2 / 40 (5.00%)	4 / 35 (11.43%)
occurrences (all)	4	2	4
Zinc deficiency			
subjects affected / exposed	2 / 52 (3.85%)	5 / 40 (12.50%)	5 / 35 (14.29%)
occurrences (all)	2	5	6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 August 2020	Version 2 of the protocol implemented changes to the enhanced liver monitoring criteria following feedback from the FDA. The study duration was revised.
03 February 2021	Version 3 of the protocol included updates to the inclusion criteria, schedule of assessments, and exploratory endpoints. Additional information and guidance on maralixibat risk and benefits was included.
06 May 2021	Version 4 of the protocol decreased the number of clinic visits. Dose escalation was revised to a 2-step schedule, when prespecified criteria were met, upon recommendation by the DMC.
25 March 2022	Version 5 of the protocol updated blood sample order and priority. The schedule of assessments was updated.
25 April 2023	Version 6 of the protocol modified and reordered objectives to reflect the sponsor's planned analyses. Safety language was updated for consistency across sponsor protocols.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported