Clinical trial results:
MRX-502: Randomized Double-blind Placebo-controlled Phase 3 Study to Evaluate the Efficacy and Safety of Maralixibat in the Treatment of Subjects with Progressive Familial Intrahepatic Cholestasis (PFIC) – MARCH-PFIC.

Summary

EudraCT number	2019-001211-22
Trial protocol	GB DE FR HU PL AT BE IT
Global end of trial date	01 September 2022

Results information

Result version number	v1 (current)
This version publication date	02 June 2023
First version publication date	02 June 2023

Trial information

Trial identification

Sponsor protocol code	MRX-502

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03905330
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Mirum Pharmaceuticals
Sponsor organisation address	950 Tower Lane, Suite 1050 , Foster City, United States, CA 94404
Public contact	Chief Scientific Officer, Mirum Pharmaceuticals, Inc. , 1 6506674085, medinfo@mirumpharma.com
Scientific contact	Chief Scientific 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-PIP03-17
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	06 December 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 September 2022
Global end of trial reached?	Yes
Global end of trial date	01 September 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of maralixibat versus placebo on the severity of pruritus in participants with PFIC2. - To evaluate the efficacy of maralixibat versus placebo on total serum bile acid (sBA) levels in participants with PFIC2 - To evaluate the efficacy of maralixibat versus placebo on the proportion of responders for the ItchRO(Obs) pruritus score in participants with PFIC2 and participants with PFIC (PFIC1, PFIC2, PFIC3, PFIC4, PFIC5, and PFIC6) - To evaluate the efficacy of maralixibat versus placebo on the sBA responder rate in participants with PFIC2 and participants with PFIC (PFIC1, PFIC2, PFIC3, PFIC4, PFIC5, and PFIC6) - To evaluate the safety, tolerability, and pharmacokinetics of maralixibat versus placebo in all participants who receive at least 1 dose of study medication.

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	17 June 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Argentina: 3
Country: Number of subjects enrolled	Brazil: 10
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Colombia: 6
Country: Number of subjects enrolled	Mexico: 9
Country: Number of subjects enrolled	Singapore: 2
Country: Number of subjects enrolled	Turkey: 2

Country: Number of subjects enrolled	Lebanon: 13
Country: Number of subjects enrolled	United States: 22
Worldwide total number of subjects	93
EEA total number of subjects	22

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)	22
Children (2-11 years)	65
Adolescents (12-17 years)	6
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 93 participants were enrolled at 29 sites in 16 countries (Argentina, Austria, Belgium, Brazil, Canada, Colombia, France, Germany, Italy, Lebanon, Mexico, Poland, Singapore, Turkey, United Kingdom, and United States).

Pre-assignment

Screening details:

The screening period starts when informed consent (or assent as applicable) is signed. The duration of the screening period is up to 6 weeks during which all procedures listed for the screening visit must be completed. A total of 125 patients were screened for the study. 32 of these patients were screen failures

Period 1

Period 1 title	Dose Escalation and stable dosing Period (overall period)
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:

After an unblinded screening period of up to 6 weeks, subjects were randomized 1:1 to receive either maralixibat or placebo. The investigator or assigned site staff will access the IRT to randomize the subject and dispense the study medication. The double-blind Dose Escalation treatment period will comprise of 4–6 weeks (maximum 6 weeks). The Baseline characteristics are taken prior to randomization.

Arms

Are arms mutually exclusive?	No
Arm title	Primary Cohort MRX

Arm description:

After an unblinded screening period of up to 6 weeks, subjects were randomized 1:1 to receive either maralixibat or placebo. The Dose Escalation period (4-6 weeks) consisted of the following weekly steps. Followed by a stable dosing period (20-22 weeks) and a 7 days Safety Follow-up period for subjects discontinuing early and for subjects not enrolling into the extension Study MRX-503

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

Dosage and administration details:

The Dose Escalation period (4-6 weeks) consisted of the following weekly steps:
• Dose level 1: 150 µg/kg maralixibat BID for 1 week
• Dose level 2: 300 µg/kg maralixibat BID for 1 week
• Dose level 3: 450 µg/kg maralixibat BID for 1 week
• Dose level 4: 600 µg/kg maralixibat BID for the remaining duration of the study
Followed by a stable dosing period (20-22 weeks)

Arm title	Primary Cohort Placebo

Arm description:

Participants received a corresponding placebo

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:

The Dose Escalation period (4-6 weeks) consisted of the following weekly steps:
• Dose level 1: 150 µg/kg placebo BID for 1 week
• Dose level 2: 300 µg/kg placebo BID for 1 week
• Dose level 3: 450 µg/kg placebo BID for 1 week
• Dose level 4: 600 µg/kg placebo BID for the remaining duration of the study
Followed by a stable dosing period (20-22 weeks)

Arm title	PFIC Cohort MRX

Arm description:

After an unblinded screening period of up to 6 weeks, subjects were randomized 1:1 to receive either maralixibat or placebo. The Dose Escalation period (4-6 weeks) consisted of the following weekly steps. Followed by a stable dosing period (20-22 weeks) and a 7 days Safety Follow-up period for subjects discontinuing early and for subjects not enrolling into the extension Study MRX-503.

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

Dosage and administration details:

The Dose Escalation period (4-6 weeks) consisted of the following weekly steps:
• Dose level 1: 150 µg/kg maralixibat BID for 1 week
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• Dose level 3: 450 µg/kg maralixibat BID for 1 week
• Dose level 4: 600 µg/kg maralixibat BID for the remaining duration of the study
Followed by a stable dosing period (20-22 weeks)

Arm title	PFIC Cohort Placebo

Arm description:

Participants received a corresponding placebo

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:

The Dose Escalation period (4-6 weeks) consisted of the following weekly steps:
• Dose level 1: 150 µg/kg placebo BID for 1 week
• Dose level 2: 300 µg/kg placebo BID for 1 week
• Dose level 3: 450 µg/kg placebo BID for 1 week
• Dose level 4: 600 µg/kg placebo BID for the remaining duration of the study
Followed by a stable dosing period (20-22 weeks)

Number of subjects in period 1	Primary Cohort MRX	Primary Cohort Placebo	PFIC Cohort MRX
Started	14	17	33
Completed	13	15	32
Not completed	1	2	1
Consent withdrawn by subject	1	1	1
Disease progression	-	1	-

Number of subjects in period 1	PFIC Cohort Placebo
Started	31
Completed	28
Not completed	3
Consent withdrawn by subject	2
Disease progression	1

Baseline characteristics

Reporting groups

Reporting group title	Dose Escalation and stable dosing Period

Reporting group description: -

Reporting group values	Dose Escalation and stable dosing Period	Total	
Number of subjects	93	93	
Age categorical			
Most participants (61 [65.6%]) were 1 to <6 years of age.			
Units: Subjects			
1 to <6 years	61	61	
6 to <13 years	26	26	
13 to 18 years	6	6	
Age continuous			
The mean (SD) age was 4.7 (3.85) years and ranged from 1 to 17 years of age.			
Units: years			
arithmetic mean	4.7		
standard deviation	± 3.85	-	
Gender categorical			
For the full cohort, there were more females (51 [54.8%]) than males (42 [45.2%])			
Units: Subjects			
Female	51	51	
Male	42	42	

Subject analysis sets

Subject analysis set title	Primary Cohort MRX
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Primary Cohort, defined as participants with genetic testing results consistent with biallelic disease-causing variation in ABCB11 (PFIC2, also referred to as BSEP deficiency), based on standard-of-care genotyping, excluding those PFIC2 participants predicted to have complete absence of BSEP function.(PFIC2 participants with heterozygosis, biliary diversion, having low or fluctuating sBA levels)

Subject analysis set title	Primary Cohort Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Primary Cohort, defined as participants with genetic testing results consistent with biallelic disease-causing variation in ABCB11 (PFIC2, also referred to as BSEP deficiency), based on standard-of-care genotyping, excluding those PFIC2 participants predicted to have complete absence of BSEP function.(PFIC2 participants with heterozygosis, biliary diversion, having low or fluctuating sBA levels)

Subject analysis set title	PFIC Cohort MRX
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Primary cohort plus PFIC1, PFIC3, PFIC4, PFIC6.

Subject analysis set title	PFIC Cohort Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Primary cohort plus PFIC1, PFIC3, PFIC4, PFIC6.

Reporting group values	Primary Cohort MRX	Primary Cohort Placebo	PFIC Cohort MRX
Number of subjects	14	17	33
Age categorical			
Most participants (61 [65.6%]) were 1 to <6 years of age.			
Units: Subjects			
1 to <6 years	9	11	22
6 to <13 years	2	5	8
13 to 18 years	3	1	3
Age continuous			
The mean (SD) age was 4.7 (3.85) years and ranged from 1 to 17 years of age.			
Units: years			
arithmetic mean	6.3	4.2	4.9
standard deviation	± 5.24	± 3.56	± 4.10
Gender categorical			
For the full cohort, there were more females (51 [54.8%]) than males (42 [45.2%])			
Units: Subjects			
Female	7	11	16
Male	7	6	17

Reporting group values	PFIC Cohort Placebo		
Number of subjects	31		
Age categorical			
Most participants (61 [65.6%]) were 1 to <6 years of age.			
Units: Subjects			
1 to <6 years	19		
6 to <13 years	11		
13 to 18 years	1		
Age continuous			
The mean (SD) age was 4.7 (3.85) years and ranged from 1 to 17 years of age.			
Units: years			
arithmetic mean	4.4		
standard deviation	± 3.61		
Gender categorical			
For the full cohort, there were more females (51 [54.8%]) than males (42 [45.2%])			
Units: Subjects			
Female	18		
Male	13		

End points

End points reporting groups

Reporting group title	Primary Cohort MRX

Reporting group description:

After an unblinded screening period of up to 6 weeks, subjects were randomized 1:1 to receive either maralixibat or placebo. The Dose Escalation period (4-6 weeks) consisted of the following weekly steps. Followed by a stable dosing period (20-22 weeks) and a 7 days Safety Follow-up period for subjects discontinuing early and for subjects not enrolling into the extension Study MRX-503

Reporting group title	Primary Cohort Placebo

Reporting group description:

Participants received a corresponding placebo

Reporting group title	PFIC Cohort MRX

Reporting group description:

After an unblinded screening period of up to 6 weeks, subjects were randomized 1:1 to receive either maralixibat or placebo. The Dose Escalation period (4-6 weeks) consisted of the following weekly steps. Followed by a stable dosing period (20-22 weeks) and a 7 days Safety Follow-up period for subjects discontinuing early and for subjects not enrolling into the extension Study MRX-503.

Reporting group title	PFIC Cohort Placebo

Reporting group description:

Participants received a corresponding placebo

Subject analysis set title	Primary Cohort MRX
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Primary Cohort, defined as participants with genetic testing results consistent with biallelic disease-causing variation in ABCB11 (PFIC2, also referred to as BSEP deficiency), based on standard-of-care genotyping, excluding those PFIC2 participants predicted to have complete absence of BSEP function.(PFIC2 participants with heterozygosis, biliary diversion, having low or fluctuating sBA levels)

Subject analysis set title	Primary Cohort Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Primary Cohort, defined as participants with genetic testing results consistent with biallelic disease-causing variation in ABCB11 (PFIC2, also referred to as BSEP deficiency), based on standard-of-care genotyping, excluding those PFIC2 participants predicted to have complete absence of BSEP function.(PFIC2 participants with heterozygosis, biliary diversion, having low or fluctuating sBA levels)

Subject analysis set title	PFIC Cohort MRX
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Primary cohort plus PFIC1, PFIC3, PFIC4, PFIC6.

Subject analysis set title	PFIC Cohort Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Primary cohort plus PFIC1, PFIC3, PFIC4, PFIC6.

Primary: Mean change in the average morning ItchRO(Obs) severity score Primary Cohort

End point title	Mean change in the average morning ItchRO(Obs) severity score Primary Cohort

End point description:

The primary efficacy endpoint is the mean change in the average morning ItchRO(Obs) severity score between baseline and Weeks 15–26, using 4-week average morning ItchRO(Obs) severity scores (Mixed Model Repeated Measures). The baseline average morning ItchRO(Obs) severity score is defined as the 4-week average morning ItchRO(Obs) severity score prior to the first dose of the study medication.

End point type	Primary

End point timeframe:

Baseline and Week 15 through Week 26, using 4-week average morning ItchRO(Obs) severity scores.

End point values	Primary Cohort MRX	Primary Cohort Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	17		
Units: Between 0-4				
least squares mean (confidence interval 95%)	-1.669 (-2.230 to -1.107)	-0.623 (-1.137 to -0.109)		

Statistical analyses

Statistical analysis title	Mean change in the average morning ItchRO(Obs)

Statistical analysis description:

The difference between maralixibat and placebo treatment groups in the mean change in the average ItchRO(Obs) severity score between baseline and Weeks 15–26

Comparison groups	Primary Cohort MRX v Primary Cohort Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0092
Method	Mixed models analysis
Parameter estimate	Least-Square mean
Point estimate	-1.046
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.811
upper limit	-0.28
Variability estimate	Standard error of the mean
Dispersion value	0.3739

Secondary: Mean change in total sBA level Primary Cohort

End point title	Mean change in total sBA level Primary Cohort

End point description:

Mean change in total sBA level between baseline and average of Weeks 18, 22, and 26

End point type	Secondary

End point timeframe:

baseline and average of Weeks 18, 22, and 26

End point values	Primary Cohort MRX	Primary Cohort Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	17		
Units: µmol/L				
least squares mean (confidence interval 95%)	-175.536 (-256.716 to -94.356)	11.187 (-58.073 to 80.446)		

Statistical analyses

Statistical analysis title	Mean Change in Total sBA Level
Comparison groups	Primary Cohort Placebo v Primary Cohort MRX
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0013
Method	Mixed models analysis
Parameter estimate	Least-Square mean
Point estimate	-186.723
Confidence interval	
level	95 %
sides	2-sided
lower limit	-293.454
upper limit	-79.992
Variability estimate	Standard error of the mean
Dispersion value	51.9501

Secondary: Mean change in the average morning ItchRO(Obs) severity score PFIC (PFIC1, PFIC2, PFIC3, PFIC4, and PFIC6)

End point title	Mean change in the average morning ItchRO(Obs) severity score PFIC (PFIC1, PFIC2, PFIC3, PFIC4, and PFIC6)

End point description:

Mean change in the average morning ItchRO(Obs) severity score between baseline and Week 15 through Week 26 in participants with PFIC (PFIC1, PFIC2, PFIC3, PFIC4, and PFIC6)

End point type	Secondary

End point timeframe:

Baseline and Week 15 through Week 26

End point values	PFIC Cohort MRX	PFIC Cohort Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	33	31		
Units: Between 0-4				
least squares mean (confidence interval 95%)	-1.787 (-2.157 to -1.418)	-0.612 (-1.004 to -0.219)		

Statistical analyses

Statistical analysis title	Mean change in the average morning ItchRO(Obs)
Statistical analysis description: PFIC Cohort	
Comparison groups	PFIC Cohort MRX v PFIC Cohort Placebo
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Least-Square mean
Point estimate	-1.176
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.707
upper limit	-0.645
Variability estimate	Standard error of the mean
Dispersion value	0.2651

Secondary: Mean change in total sBA level PFIC (PFIC1, PFIC2, PFIC3, PFIC4, and PFIC6)

End point title	Mean change in total sBA level PFIC (PFIC1, PFIC2, PFIC3, PFIC4, and PFIC6)
End point description: Mean change in total sBA level between baseline and average of Weeks 18, 22, and 26 in participants with PFIC (PFIC1, PFIC2, PFIC3, PFIC4, and PFIC6)	
End point type	Secondary
End point timeframe: baseline and average of Weeks 18, 22, and 26	

End point values	PFIC Cohort MRX	PFIC Cohort Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	31		
Units: µmol/L				
least squares mean (confidence interval 95%)	-157.489 (-200.276 to -114.703)	2.913 (-42.320 to 48.146)		

Statistical analyses

Statistical analysis title	Mean Change in Total sBA Level
Comparison groups	PFIC Cohort MRX v PFIC Cohort Placebo
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Least-Square mean
Point estimate	-160.403
Confidence interval	
level	95 %
sides	2-sided
lower limit	-220.836
upper limit	-99.97
Variability estimate	Standard error of the mean
Dispersion value	30.1827

Secondary: Proportion of ItchRO(Obs) responders Primary Cohort	
End point title	Proportion of ItchRO(Obs) responders Primary Cohort
End point description:	
Proportion of ItchRO(Obs) responders from Week 15 to Week 26 in participants with PFIC2 using the average value from the three 4-week periods (Weeks 15-18, 19-22, and 23-26). The number in the Subject Analysis Set refers to the number of responders.	
End point type	Secondary
End point timeframe:	
Week 15 to Week 26 using the average value from the three 4-week periods (Weeks 15-18, 19-22, and 23-26)	

End point values	Primary Cohort MRX	Primary Cohort Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	17		
Units: Number of responders	8	4		

Statistical analyses

Statistical analysis title	Proportion of ItchRO responders
Comparison groups	Primary Cohort MRX v Primary Cohort Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0736
Method	Barnard's exact test

Secondary: Proportion of sBA responders Primary Cohort

End point title	Proportion of sBA responders Primary Cohort

End point description:

Proportion of sBA responders from Week 18 to Week 26 in participants with PFIC2, using the average value from Weeks 18, 22, and 26 values. The number in the Subject Analysis Set refers to the number of responders.

End point type	Secondary

End point timeframe:

Awerage value from Weeks 18, 22, and 26

End point values	Primary Cohort MRX	Primary Cohort Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	17		
Units: Number of responders	7	1		

Statistical analyses

Statistical analysis title	Proportion of sBA responders
Comparison groups	Primary Cohort MRX v Primary Cohort Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0047
Method	Barnard's exact test

Secondary: Proportion of ItchRO(Obs) responders PFIC (PFIC1, PFIC2, PFIC3, PFIC4, and PFIC6)

End point title	Proportion of ItchRO(Obs) responders PFIC (PFIC1, PFIC2, PFIC3, PFIC4, and PFIC6)

End point description:

Proportion of ItchRO(Obs) responders from Week 15 to Week 26 in participants with PFIC (PFIC1, PFIC2, PFIC3, PFIC4, and PFIC6). The number in the Subject Analysis Set refers to the number of responders.

End point type	Secondary

End point timeframe:
From Week 15 to Week 26

End point values	PFIC Cohort MRX	PFIC Cohort Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	33	31		
Units: Number of responders	21	8		

Statistical analyses

Statistical analysis title	Proportion of ItchRO(Obs) responders
Comparison groups	PFIC Cohort MRX v PFIC Cohort Placebo
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0023
Method	Barnard's exact test

Secondary: Proportion of sBA responders PFIC (PFIC1, PFIC2, PFIC3, PFIC4, and PFIC6)

End point title	Proportion of sBA responders PFIC (PFIC1, PFIC2, PFIC3, PFIC4, and PFIC6)

End point description:

Proportion of sBA responders from Week 18 to Week 26 in participants with PFIC (PFIC1, PFIC2, PFIC3, PFIC4, and PFIC6). The number in the Subject Analysis Set refers to the number of responders.

End point type	Secondary

End point timeframe:
Week 18 to Week 26

End point values	PFIC Cohort MRX	PFIC Cohort Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	33	31		
Units: Number of responders	17	2		

Statistical analyses

Statistical analysis title	Proportion of sBA responders
Comparison groups	PFIC Cohort Placebo v PFIC Cohort MRX

Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Barnard's exact test

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline to EOT	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups	
Reporting group title	Safety Population
Reporting group description:	
All participants who received at least 1 dose of study drug.	

Serious adverse events	Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 93 (8.60%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Accidental exposure to product			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Coagulopathy			

subjects affected / exposed	1 / 93 (1.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Idiopathic pneumonia syndrome			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	2 / 93 (2.15%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis viral			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Vitamin K deficiency			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	90 / 93 (96.77%)		
Investigations			
Blood bilirubin increased			
alternative assessment type: Systematic			
subjects affected / exposed	10 / 93 (10.75%)		
occurrences (all)	11		
Alanine aminotransferase increased			
alternative assessment type: Systematic			
subjects affected / exposed	9 / 93 (9.68%)		
occurrences (all)	10		
Vitamin E decreased			
alternative assessment type: Systematic			
subjects affected / exposed	7 / 93 (7.53%)		
occurrences (all)	7		
Vitamin D decreased			
alternative assessment type: Systematic			
subjects affected / exposed	6 / 93 (6.45%)		
occurrences (all)	6		
International normalised ratio increased			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 93 (5.38%)		
occurrences (all)	6		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	30 / 93 (32.26%)		
occurrences (all)	39		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	36 / 93 (38.71%)		
occurrences (all)	67		
Abdominal pain			

subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all)	13 / 93 (13.98%) 20 8 / 93 (8.60%) 10 6 / 93 (6.45%) 7 6 / 93 (6.45%) 7		
Hepatobiliary disorders Hyperbilirubinaemia alternative assessment type: Systematic subjects affected / exposed occurrences (all)	 5 / 93 (5.38%) 5		
Respiratory, thoracic and mediastinal disorders Rhinorrhoea alternative assessment type: Systematic subjects affected / exposed occurrences (all) Cough alternative assessment type: Systematic subjects affected / exposed occurrences (all)	 13 / 93 (13.98%) 16 12 / 93 (12.90%) 17		
Skin and subcutaneous tissue disorders Pruritus alternative assessment type: Systematic subjects affected / exposed occurrences (all)	 13 / 93 (13.98%) 15		
Infections and infestations Upper respiratory tract infection alternative assessment type: Systematic subjects affected / exposed occurrences (all) Influenza	 9 / 93 (9.68%) 16		

alternative assessment type: Systematic subjects affected / exposed occurrences (all) Coronavirus infection alternative assessment type: Systematic subjects affected / exposed occurrences (all) Nasopharyngitis alternative assessment type: Systematic subjects affected / exposed occurrences (all) Gastroenteritis alternative assessment type: Systematic subjects affected / exposed occurrences (all)	8 / 93 (8.60%) 11 7 / 93 (7.53%) 8 7 / 93 (7.53%) 11 5 / 93 (5.38%) 6		
Metabolism and nutrition disorders Vitamin D deficiency alternative assessment type: Systematic subjects affected / exposed occurrences (all) Vitamin E deficiency alternative assessment type: Systematic subjects affected / exposed occurrences (all)	8 / 93 (8.60%) 10 7 / 93 (7.53%) 7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 April 2019	To avoid the inclusion of subjects with a mild or intermittent from of cholestasis, the Inclusion Criteria 6 and Exclusion Criteria 1 were amended with further clarification on the expectation of Chronic nature of cholestasis for subjects to be allowed in the study, as well as further clarification for the supplemental cohort. On top of that, changes to clarify and align the timing of pregnancy testing in different sections of the protocol were made .
22 November 2019	In order to improve the safety of study participants and to reflect other changes in the protocol, an urinary pregnancy test was added to visit 4,6 and 8, as well as a PIC and CIC to EOT/ET, a clinical scratch scale to the screening and a Lipid Panel. Furthermore, Exclusion Criteria# 2 (to exclude subjects with recurrent intrahepatic cholestasis to avoid enrolling subjects who have intermittent spontaneous near-normalization of pruritus and sBA or remission of peritus), Exclusion Criteria #3 (Exclusion of subjects with pruritus of non-cholestatic origins, as this would directly confound the primary endpoint of the study.), and a questionnaire as an anchor for further ItchRo validation were added to the Protocol. Further Clarifications were also provided for, Exclusion Criteria #6 (Patients should not be excluded unless they have an imminent need for liver transplant.), Exclusion criteria # 11 (Excusing patients with possible malignant liver mass.), for when subjects should be discontinued (Subjects should only be discontinued if there is an imminent need for a liver transplant.), and of the permitted dose adaptations for permitted treatments (Dose adaptations of permitted treatments are allowed if the body weight changes during the study.), as well as updates on the volume of blood that is to be drawn. Finally, the option of long-term follow-up on disease progression for subjects who discontinue prematurely, the clarification that subjects should be informed about the extension study MRX-503 prior to Visit 9, and the correction of inconsistency in the duration for which female subjects should use contraception after their last dose of study medication were added.
16 June 2020	Various texts were added, revised, and deleted in order to provide reference to the appendix for management of study procedures during the global pandemic, allow subjects to meet inclusion age criterion by baseline to allow for earlier screening of subjects, clarify that criterion only applies to the primary cohort, clarify that subjects must have pruritus to be eligible, include subjects with intermittent cholestasis in the supplemental cohort, exclude any phenylbuterates, deleted criterion for exclusion of administration of growth hormones, instruct sites to follow country-specific guidelines for acceptable methods of contraception, update the description of study medication packaging to current form, revise limit of propylene glycol exposure(the maximum aily exposure stated in the study protocol is 25mg/kg/day; after recalculation, the maximum may be ≤26 mg/kg/day for BID dosing), and to add expedited safety reporting as a reason for unblinding of treatment assignment.
10 May 2022	Changes made to the Protocol include, clarifying the rational of the Study, updating the secondary objectives and endpoints, as well as the exploratory objectives and endpoints to better capture clinically meaningful measures in the primary cohort and the broader PFIC population, specifying that the SAP will detail how the assignment of siblings occurs, including a blinded validation analysis of the ItchRO to confirm the responder definition, clarifying sample size calculation and that the ITT population will include all randomized subjects, defining of analysis groups, clarifying the scoring of ItchRO(Obs) and ItchRO(Pt) severity scores, and how to construct monthly scores, Updating the hypothesis tests to be performed due to the adjustment of the secondary endpoint, and finally providing guidance regarding COVID-19 vaccinations.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported