Clinical trial results:
A Multicentre Extension Study to Evaluate the Long-Term Safety and Durability of the Therapeutic Effect of LUM001, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), in the Treatment of Cholestatic Liver Disease in Pediatric Subjects with Alagille Syndrome

Summary

EudraCT number	2013-003832-54
Trial protocol	GB
Global end of trial date	17 June 2020

Results information

Result version number	v1 (current)
This version publication date	27 December 2020
First version publication date	27 December 2020
Summary attachment (see zip file)	Synoptic Clinical Study Report (lum001-303-synopsis-csr.pdf) Interim Clinical Study Report Synopsis (synopsis-interim.pdf)

Trial information

Trial identification

Sponsor protocol code	LUM001-303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02047318
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Mirum Pharmaceuticals, Inc.
Sponsor organisation address	950 Tower Lane, Suite 1050, Foster City, United States, CA 94404
Public contact	Medical Information Mirum, Mirum Pharmaceuticals, Inc., 1 6506674085, medinfo@mirumpharma.com
Scientific contact	Medical Information Mirum, 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	17 September 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 October 2015
Global end of trial reached?	Yes
Global end of trial date	17 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective (up to and including Week 72) was to evaluate the long-term safety and tolerability of maralixibat (MRX) in pediatric patients with Alagille Syndrome.
The secondary objectives (up to and including Week 72) were to evaluate the long-term effects of MRX on serum bile acids, pruritus, and xanthomas; and to explore the long-term effects of MRX on other biochemical markers of cholestasis and liver disease, and an expanded dosing range to identify doses necessary to achieve the optimal benefit-to-risk ratio for this patient population.
The objectives of the long-term follow-up treatment period for participants who were eligible for Protocol Amendment 5 were to offer eligible participants in the LUM001-303 study continued study treatment; explore a twice daily (BID) dosing regimen and higher daily dosing of MRX; obtain safety and efficacy data in participants treated long-term on MRX; assess the level of alpha-fetoprotein; assess palatability of the MRX formulation.

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	20 December 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
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	United Kingdom: 19
Worldwide total number of subjects	19
EEA total number of subjects	19

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)	2
Children (2-11 years)	13
Adolescents (12-17 years)	4
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 19 participants were enrolled in the core study (Day 1 to Week 72) and treated in the study. Completion of participation in Study LUM001-302 was an inclusion criterion for this study: 5 of the 19 participants had received placebo in Study LUM001-302; and 14 of the 19 participants had received any dose level of MRX in Study LUM001-302.

Pre-assignment

Screening details:

All patients who were screened for the study were enrolled. One subject who completed participation in Study LUM001-302 (and received placebo) did not enter Study LUM001-303.

Period 1

Period 1 title	Core study period
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Although all participants were treated with MRX, dose optimization occurred in a blinded, titrated manner based on randomization in the LUM001-302 core study. This represented a real dose escalation for participants previously randomized to placebo and a mock dose escalation for participants previously randomized to active study treatment in the LUM001-302 core study.

Arms

Arm title	Core study period

Arm description:

In the lead-in Study LUM001-302, participants were randomized to receive either placebo or active drug (MRX). The last observation obtained before first dose of MRX (either for participants who received MRX in Study LUM001-302 or in Study LUM001-303 for participants who received placebo in Study LUM001-302) was used as the MRX baseline observation for all calculations of change from MRX baseline. For participants who were assigned MRX in Study LUM001-302, results at each post-baseline analysis visit included up to 13 more weeks of treatment than participants who were assigned placebo in Study LUM001-302.
The core study period of Study LUM001-303 was from Day 1 to Week 72. It encompassed:
- a 4-week double-blind dose-escalation period
- an 8-week dose-optimization period
- a 60-week stable dosing period

All participants received MRX.

Arm type	Experimental
Investigational medicinal product name	Maralixibat chloride
Investigational medicinal product code	
Other name	LUM001
Pharmaceutical forms	Powder and solvent for oral solution
Routes of administration	Oral use

Dosage and administration details:

During the 4-week double-blind dose-escalation period participants who received placebo during Study LUM001-302 received weekly dose increases of MRX up to a target dose of 140 µg/kg once daily (QD); and participants who received MRX during Study LUM001-302 continued to receive the dose of MRX that they were taking at Week 13 of Study LUM001-302.
During the 8-week dose-optimization period MRX dosing could be adjusted by the investigator to achieve optimal control of pruritus at a dose level tolerated by the participant up to a maximum dose of MRX 280 µg/kg QD. Dose levels during the period were 35, 70, 140, or 280 µg/kg QD.
During the 60-week stable dosing period participants were dosed with the Week 12 dose, or the highest tolerated dose below the Week 12 dose.

Number of subjects in period 1	Core study period
Started	19
Completed	7
Not completed	12
Withdrawal by caregiver	3
Adverse event, serious non-fatal	1
Did not consent to 52-week follow-up	8

Period 2

Period 2 title	52-week follow-up treatment period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

All participants continued to receive MRX. Participants, investigators, and study site personnel remained blinded to all participants' treatment assignments from the LUM001-302 core study.

Arms

Arm title	52-week follow-up treatment period

Arm description:

At Week 72, participants were assessed by the investigator to determine their willingness and eligibility to roll over into the 52-week follow-up treatment period to receive MRX at the doses they were receiving at Week 72.
Note: one subject who completed the original study through Week 72 did not consent to protocol amendment 4, and so did not participate in the 52-week follow-up treatment period.

Arm type	Experimental
Investigational medicinal product name	Maralixibat chloride
Investigational medicinal product code	
Other name	LUM001
Pharmaceutical forms	Powder and solvent for oral solution
Routes of administration	Oral use

Dosage and administration details:

For participants whose caregivers did not wish the participants to enter the follow-up treatment period, or who were not eligible to enter the follow-up treatment period, a safety follow-up phone call was made by the study site 30 days after the last dose of MRX. If any participant experienced intolerance, the investigator, in consultation with the medical monitor, could lower the dose to a previously tolerated dose at any time during the entire follow-up treatment period.

Number of subjects in period 2[1]	52-week follow-up treatment period
Started	6
Completed	6

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: One subject completed the original study, through Week 72, and reconsented only to protocol amendment 5, the long-term follow-up treatment period. This subject did not participate in the 52-week follow-up treatment period.

Period 3

Period 3 title	Long-term follow-up treatment period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

All participants continued to receive MRX. Participants, investigators, and study site personnel remained blinded to all participants' treatment assignments from Study LUM001-302.

Arms

Arm title	Long-term follow-up treatment period

Arm description:

The long-term follow-up treatment period was for eligible participants who chose to stay on treatment with MRX. Participants were considered eligible if they:
- completed the protocol through either the Week 124 or the Early Termination visit
- completed the protocol with no major safety concerns
- discontinued due to safety reasons judged unrelated to the MRX
- laboratory results returned to levels acceptable for this patient population
- did not meet any of the protocol’s stopping rules at the time of entry into the follow-up period
Participation in the long-term follow-up treatment period continued until either: 1) the participants were eligible to enter another MRX study; 2) MRX was available commercially; or 3) the sponsor stopped the program or development in this indication.
Note: one participant who completed the core study period did not consent to the 52-week follow-up treatment period. They reconsented to protocol amendment 5 and joined the long-term follow-up.

Arm type	Experimental
Investigational medicinal product name	Maralixibat chloride
Investigational medicinal product code	
Other name	LUM001
Pharmaceutical forms	Powder and solvent for oral solution
Routes of administration	Oral use

Dosage and administration details:

During the long-term follow-up treatment period, participants could have their dose of MRX increased to a maximum of 560 µg/kg QD (280 µg/kg twice daily [BID]), based on efficacy (sBA and ItchRO score) and safety assessment results. If any participant experienced intolerance, the investigator, in consultation with the medical monitor, could lower the dose to a previously tolerated dose at any time during the entire follow-up treatment period.

Number of subjects in period 3	Long-term follow-up treatment period
Started	6
Completed	6
Not completed	1
Consent withdrawn by subject	1
Joined	1
Consented to long-term follow-up but not 52-week	1

Baseline characteristics

Reporting groups

Reporting group title	Core study period

Reporting group description: -

Reporting group values	Core study period	Total	
Number of subjects	19	19	
Age categorical			
The last observation obtained before the first dose of MRX (whether before receiving MRX in Study LUM001-302 for participants who received MRX in Study LUM001-302, or in Study LUM001-303 for participants who received placebo in Study LUM001-302) was used as the MRX baseline observation. In the overall population, the mean (SD) age at MRX baseline was 6.0 (5.02) years, and participants ranged from 1 to 16 years of age.			
Units: Subjects			
<2 years	3	3	
2 to 4 years	6	6	
5 to 8 years	5	5	
9 to 12 years	2	2	
13 to 18 years	3	3	
Gender categorical			
Units: Subjects			
Female	9	9	
Male	10	10	
Race			
Units: Subjects			
Asian	1	1	
Black or African American	1	1	
White	16	16	
More than one race	1	1	
Height z-score			
The last observation obtained before the first dose of MRX (whether before receiving MRX in Study LUM001-302 for participants who received MRX in Study LUM001-302, or in Study LUM001-303 for participants who received placebo in Study LUM001-302) was used as the MRX baseline observation.			
Units: z-score			
arithmetic mean	-1.850		
standard deviation	± 1.3095	-	
Weight z-score			
The last observation obtained before the first dose of MRX (whether before receiving MRX in Study LUM001-302 for participants who received MRX in Study LUM001-302, or in Study LUM001-303 for participants who received placebo in Study LUM001-302) was used as the MRX baseline observation.			
Units: z-score			
arithmetic mean	-1.565		
standard deviation	± 1.0221	-	

End points

End points reporting groups

Reporting group title	Core study period

Reporting group description:

In the lead-in Study LUM001-302, participants were randomized to receive either placebo or active drug (MRX). The last observation obtained before first dose of MRX (either for participants who received MRX in Study LUM001-302 or in Study LUM001-303 for participants who received placebo in Study LUM001-302) was used as the MRX baseline observation for all calculations of change from MRX baseline. For participants who were assigned MRX in Study LUM001-302, results at each post-baseline analysis visit included up to 13 more weeks of treatment than participants who were assigned placebo in Study LUM001-302.
The core study period of Study LUM001-303 was from Day 1 to Week 72. It encompassed:
- a 4-week double-blind dose-escalation period
- an 8-week dose-optimization period
- a 60-week stable dosing period
All participants received MRX.

Reporting group title	52-week follow-up treatment period

Reporting group description:

At Week 72, participants were assessed by the investigator to determine their willingness and eligibility to roll over into the 52-week follow-up treatment period to receive MRX at the doses they were receiving at Week 72.
Note: one subject who completed the original study through Week 72 did not consent to protocol amendment 4, and so did not participate in the 52-week follow-up treatment period.

Reporting group title	Long-term follow-up treatment period

Reporting group description:

The long-term follow-up treatment period was for eligible participants who chose to stay on treatment with MRX. Participants were considered eligible if they:
- completed the protocol through either the Week 124 or the Early Termination visit
- completed the protocol with no major safety concerns
- discontinued due to safety reasons judged unrelated to the MRX
- laboratory results returned to levels acceptable for this patient population
- did not meet any of the protocol's stopping rules at the time of entry into the follow-up period
Participation in the long-term follow-up treatment period continued until either: 1) the participants were eligible to enter another MRX study; 2) MRX was available commercially; or 3) the sponsor stopped the program or development in this indication.
Note: one participant who completed the core study period did not consent to the 52-week follow-up treatment period. They reconsented to protocol amendment 5 and joined the long-term follow-up.

Subject analysis set title	Core study period: MRX baseline values
Subject analysis set type	Sub-group analysis

Subject analysis set description:

These are the MRX baseline values for participants. The last observation obtained before the first dose of MRX (whether before receiving MRX in Study LUM001-302 for participants who received MRX in Study LUM001-302, or in Study LUM001-303 for participants who received placebo in Study LUM001-302) was used as the MRX baseline observation for all calculations of change from MRX baseline. For participants who were assigned MRX in Study LUM001-302, results at each post-baseline analysis visit included up to 13 more weeks of treatment than participants who were assigned placebo in Study LUM001-302.

Subject analysis set title	Core study period: Week 48 values
Subject analysis set type	Sub-group analysis

Subject analysis set description:

These are the Week 48 values for participants. These participants are also represented in the Core study period: MRX baseline values group; the analyses look at the change from MRX baseline to Week 48 in the same participants.

Subject analysis set title	Week 252 values
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Week 252 values for participants continuing in the study. These participants are also represented in the Core study period: MRX baseline values group; the analyses look at the change from MRX baseline to Week 252 in the same participants.

Subject analysis set title	Week 158 values

Subject analysis set type	Sub-group analysis

Subject analysis set description:

Week 158 values for participants continuing in the study. These participants are also represented in the Core study period: MRX baseline values group; the analyses look at the change from MRX baseline to Week 158 in the same participants.

Primary: Change from MRX baseline to Week 48 in fasting sBA levels

End point title	Change from MRX baseline to Week 48 in fasting sBA levels

End point description:

The primary endpoint of this study was the mean change from MRX baseline to Week 48 in fasting sBA level. The primary objective was defined as "up to and including Week 72" while the primary endpoint evaluated the change from baseline to Week 48. Results reported here are for the Week 48 endpoint.

End point type	Primary

End point timeframe:

MRX baseline to Week 48

End point values	Core study period: MRX baseline values	Core study period: Week 48 values		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19[1]	17[2]		
Units: µmol/L				
arithmetic mean (standard deviation)	261.96 (± 206.839)	128.32 (± 101.742)		

Notes:

[1] - Data collected from 19 participants at MRX baseline.

[2] - Data collected at Week 48 from 17 of the 19 participants who contributed values at MRX baseline.

Statistical analyses

Statistical analysis title	Change from MRX baseline to Week 48 in sBA

Statistical analysis description:

This analysis investigated whether a statistically significant change in sBA levels was observed when comparing MRX baseline to Week 48. The analysis was based on the safety population.

Comparison groups	Core study period: MRX baseline values v Core study period: Week 48 values
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[3]
P-value	= 0.0012 [4]
Method	Student's t-test
Parameter estimate	Mean difference (net)
Point estimate	-94.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-145.26
upper limit	-43.55
Variability estimate	Standard deviation
Dispersion value	98.915

Notes:

[3] - The null hypothesis that the mean change was equal to zero was tested using the Student’s t-test to determine if the mean change in sBA levels between MRX baseline and Week 48 was statistically significant.

[4] - Data for this analysis were obtained from 19 participants at MRX baseline; 17 of those participants contributed Week 48 data.

Secondary: Change from MRX baseline over time in fasting sBA levels

End point title	Change from MRX baseline over time in fasting sBA levels

End point description:

This secondary efficacy endpoint is the mean change from MRX baseline over time in fasting sBA levels. The secondary objectives were defined as “up to and including Week 72” while the endpoints evaluated the change from baseline to Week 48. Results reported here are the long-term results, including Week 72 and subsequent visits.

End point type	Secondary

End point timeframe:

MRX baseline to EOT

End point values	Core study period: MRX baseline values	Week 252 values		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19[5]	6[6]		
Units: µmol/L				
arithmetic mean (standard deviation)	261.96 (± 206.839)	118.32 (± 76.140)		

Notes:

[5] - Data collected from 19 participants at MRX baseline.

[6] - Data collected at Week 252 from all 6 participants who contributed values at MRX baseline.

Statistical analyses

Statistical analysis title	Change from MRX baseline over time in sBA

Statistical analysis description:

This analysis investigated whether a statistically significant change in sBA levels was observed over time (with Week 252 chosen as the end point, as the last analysis visit with at least 6 participants). The analysis was based on the safety population.

Comparison groups	Core study period: MRX baseline values v Week 252 values
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	equivalence[7]
P-value	= 0.032 [8]
Method	Student's t-test
Parameter estimate	Mean difference (net)
Point estimate	-141.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-265.77
upper limit	-18.12
Variability estimate	Standard deviation
Dispersion value	117.992

Notes:

[7] - The null hypothesis that the mean change was equal to zero was tested using the Student's t-test to determine if the mean change in sBA levels from baseline over time (to Week 252) was statistically significant.

[8] - Data for this analysis were obtained from 19 participants at MRX baseline; 6 of those participants contributed Week 252 data.

Secondary: Change from MRX baseline to Week 48 in pruritus

End point title	Change from MRX baseline to Week 48 in pruritus

End point description:

This secondary efficacy endpoint is the change from MRX baseline to Week 48 in pruritus as measured by ItchRO(Obs) weekly average morning severity score. ItchRO scores range from 0 to 4; the higher score indicates increasing itch severity (0 = none; 4 = very severe). The secondary objectives were defined as "up to and including Week 72" while the endpoints evaluate the change from baseline to Week 48. Results reported here are for the Week 48 endpoint.

End point type	Secondary

End point timeframe:

MRX baseline to Week 48

End point values	Core study period: MRX baseline values	Core study period: Week 48 values		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19[9]	17[10]		
Units: Points (0-4)				
arithmetic mean (standard deviation)	2.435 (± 0.7952)	1.307 (± 0.6995)		

Notes:

[9] - Values were collected from 19 participants at MRX baseline.

[10] - Data collected at Week 48 from 17 of the 19 participants who contributed values at MRX baseline.

Statistical analyses

Statistical analysis title	Change from MRX baseline to Week 48 in ItchRO(Obs)

Statistical analysis description:

This analysis investigated whether a statistically significant change in ItchRO(Obs) scores was observed when comparing MRX baseline to Week 48. The analysis was based on the safety population.

Comparison groups	Core study period: MRX baseline values v Core study period: Week 48 values
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[11]
P-value	< 0.0001 [12]
Method	Student's t-test
Parameter estimate	Mean difference (net)
Point estimate	-1.095
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.464
upper limit	-0.726
Variability estimate	Standard deviation
Dispersion value	0.7173

Notes:

[11] - The null hypothesis that the mean change was equal to zero was tested using the Student's t-test to determine if the mean change in sBA levels between MRX baseline and Week 48 was statistically significant.

[12] - Data for this analysis were obtained from 19 participants at MRX baseline; 17 of those participants contributed Week 48 data.

Secondary: Change from MRX baseline over time in pruritus

End point title	Change from MRX baseline over time in pruritus

End point description:

This secondary efficacy endpoint is the change from MRX baseline over time in pruritus as measured by ItchRO(Obs) weekly average morning severity score. ItchRO scores range from 0 to 4; the higher score indicates increasing itch severity (0 = none; 4 = very severe). The secondary objectives were defined as "up to and including Week 72" while the endpoints evaluated the change from baseline to Week 48. Results reported here are the long-term results, including Week 72 and subsequent visits.

End point type	Secondary

End point timeframe:

MRX baseline to EOT

End point values	Core study period: MRX baseline values	Week 158 values		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19[13]	6[14]		
Units: Points (0-4)				
arithmetic mean (standard deviation)	2.435 (± 0.7952)	0.952 (± 0.4302)		

Notes:

[13] - Data collected from 19 participants at MRX baseline

[14] - Data collected at Week 158 from all 6 participants who contributed values at MRX baseline.

Statistical analyses

Statistical analysis title	Change from MRX baseline over time in ItchRO(Obs)

Statistical analysis description:

This analysis investigated whether a statistically significant change in ItchRO(Obs) scores was observed over time (with Week 158 chosen as the end point, as the last analysis visit with at least 6 participants). The analysis was based on the safety population.

Comparison groups	Core study period: MRX baseline values v Week 158 values
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	equivalence[15]
P-value	= 0.0307 [16]
Method	Student's t-test
Parameter estimate	Mean difference (net)
Point estimate	-0.958
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.784
upper limit	-0.132

Variability estimate	Standard deviation
Dispersion value	0.7868

Notes:

[15] - The null hypothesis that the mean change was equal to zero was tested using the Student’s t-test to determine if the mean change in ItchRO(Obs) scores from baseline over time (to Week 158) was statistically significant.

[16] - Data for this analysis were obtained from 19 participants at MRX baseline; 6 of those participants contributed Week 158 data.

Secondary: Change from MRX baseline to Week 48 in clinician xanthoma severity score

End point title	Change from MRX baseline to Week 48 in clinician xanthoma severity score

End point description:

This secondary efficacy endpoint is the mean change from MRX baseline to Week 48 in clinician xanthoma severity scores. It is based on a 0-4 scale to rate the number of lesions present and the degree to which the participant's lesions interfere or limit his or her activities. Clinician xanthoma severity scores range from 0 to 4, with a xanthoma score of zero representing no evidence of xanthomatosis and a score of 4 representing xanthoma so severe that it is disabling. Clinician xanthoma severity scores were not assessed in Study LUM001-302 so mean clinician xanthoma severity score at MRX baseline was calculated from the 5 participants who were assigned to placebo in Study LUM001-302, and analysis of change from MRX baseline is not presented. The secondary objectives were defined as “up to and including Week 72” while the endpoints evaluate the change from baseline to Week 48. Results reported here are for the Week 48 endpoint.

End point type	Secondary

End point timeframe:

MRX baseline to Week 48

End point values	Core study period: MRX baseline values	Core study period: Week 48 values		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5[17]	17[18]		
Units: Points (0-4)				
arithmetic mean (standard deviation)	0.4 (± 0.55)	0.2 (± 0.73)		

Notes:

[17] - Mean MRX baseline scores were calculated from the 5 participants assigned placebo in LUM001-302.

[18] - Mean MRX Week 48 scores were calculated from 17 participants.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from MRX baseline over time in clinician xanthoma severity score

End point title	Change from MRX baseline over time in clinician xanthoma severity score

End point description:

This secondary efficacy endpoint is the mean change from MRX baseline over time (with Week 252 chosen as the end point, as the last analysis visit with at least 6 participants) in clinician xanthoma severity scores. It is based on a 0-4 scale to rate the number of lesions present and the degree to which the lesions interfere or limit activities. Clinician xanthoma severity scores range from 0 to 4, with a score of zero representing no evidence of xanthomatosis and a score of 4 representing xanthoma so severe that it is disabling. Clinician xanthoma severity scores were not assessed in Study LUM001-302

so mean clinician xanthoma severity score at MRX baseline was calculated from the 5 participants assigned to placebo in Study LUM001-302, and analysis of change from MRX baseline is not presented. The secondary objectives were defined as "up to and including Week 72" while the endpoints evaluated the change from baseline to Week 48. Results reported here are the long-term results.

End point type	Secondary

End point timeframe:

MRX baseline to EOT

End point values	Core study period: MRX baseline values	Week 252 values		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5[19]	6[20]		
Units: Points (0-4)				
arithmetic mean (standard deviation)	0.4 (± 0.55)	0.2 (± 0.41)		

Notes:

[19] - Mean MRX baseline scores were calculated from the 5 participants assigned placebo in LUM001-302.

[20] - Mean Week 252 scores were calculated from 6 participants.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from MRX baseline to Week 48 in alkaline phosphatase

End point title	Change from MRX baseline to Week 48 in alkaline phosphatase

End point description:

This secondary efficacy endpoint is the mean change from MRX baseline to Week 48 in ALP. The secondary objectives were defined as "up to and including Week 72" while the endpoints evaluate the change from baseline to Week 48. Results reported here are for the Week 48 endpoint.

End point type	Secondary

End point timeframe:

MRX baseline to Week 48

End point values	Core study period: MRX baseline values	Core study period: Week 48 values		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19[21]	17[22]		
Units: U/L				
arithmetic mean (standard deviation)	601.5 (± 232.54)	596.2 (± 185.20)		

Notes:

[21] - Data collected from 19 participants at MRX baseline.

[22] - Data collected at Week 48 from 17 of the 19 participants who contributed values at MRX baseline.

Statistical analyses

Statistical analysis title	Change from MRX baseline to Week 48 in ALP

Statistical analysis description:

This analysis investigated whether a statistically significant change in ALP levels was observed when comparing MRX baseline to Week 48. The analysis was based on the safety population.

Comparison groups	Core study period: MRX baseline values v Core study period: Week 48 values
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[23]
P-value	= 0.8863 [24]
Method	Student's t-test
Parameter estimate	Mean difference (net)
Point estimate	7.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-100.7
upper limit	115.6
Variability estimate	Standard deviation
Dispersion value	210.32

Notes:

[23] - The null hypothesis that the mean change was equal to zero was tested using the Student's t-test to determine if the mean change in ALP levels between MRX baseline and Week 48 was statistically significant.

[24] - Data for this analysis were obtained from 19 participants at MRX baseline; 17 of those participants contributed Week 48 data.

Secondary: Change from MRX baseline over time in alkaline phosphatase

End point title	Change from MRX baseline over time in alkaline phosphatase

End point description:

This secondary efficacy endpoint is the mean change from MRX baseline over time in ALP. The secondary objectives were defined as "up to and including Week 72" while the endpoints evaluated the change from baseline to Week 48. Results reported here are the long-term results, including Week 72 and subsequent visits.

End point type	Secondary

End point timeframe:

MRX baseline to EOT

End point values	Core study period: MRX baseline values	Week 252 values		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19[25]	6[26]		
Units: U/L				
arithmetic mean (standard deviation)	601.5 (± 232.54)	430.5 (± 223.56)		

Notes:

[25] - Data collected from 19 participants at MRX baseline.

[26] - Data collected at Week 252 from 6 participants who contributed values at MRX baseline.

Statistical analyses

Statistical analysis title	Change from MRX baseline over time in ALP

Statistical analysis description:

This analysis investigated whether a statistically significant change in ALP levels was observed over time (with Week 252 chosen as the end point as the last analysis visit with at least 6 participants). The analysis was based on the safety population.

Comparison groups	Core study period: MRX baseline values v Week 252 values
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	equivalence[27]
P-value	= 0.22 [28]
Method	Student's t-test
Parameter estimate	Mean difference (net)
Point estimate	-184.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-522.5
upper limit	153.8
Variability estimate	Standard deviation
Dispersion value	322.22

Notes:

[27] - The null hypothesis that the mean change was equal to zero was tested using the Student's t-test to determine if the mean change in ALP levels from baseline over time (to Week 252) was statistically significant.

[28] - Data for this analysis were obtained from 19 participants at MRX baseline; 6 of those participants contributed Week 252 data.

Secondary: Change from MRX baseline to Week 48 in alanine aminotransferase

End point title	Change from MRX baseline to Week 48 in alanine aminotransferase

End point description:

This secondary efficacy endpoint is the mean change from MRX baseline to Week 48 in ALT. The secondary objectives were defined as "up to and including Week 72" while the endpoints evaluate the change from baseline to Week 48. Results reported here are for the Week 48 endpoint.

End point type	Secondary

End point timeframe:

MRX baseline to Week 48

End point values	Core study period: MRX baseline values	Core study period: Week 48 values		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19[29]	17[30]		
Units: U/L				
arithmetic mean (standard deviation)	130.7 (± 59.12)	174.5 (± 97.28)		

Notes:

[29] - Data collected from 19 participants at MRX baseline.

[30] - Data collected at Week 48 from 17 of the 19 participants who contributed values at MRX baseline.

Statistical analyses

Statistical analysis title	Change from MRX baseline to Week 48 in ALT

Statistical analysis description:

This analysis investigated whether a statistically significant change in ALT levels was observed when comparing MRX baseline to Week 48. The analysis was based on the safety population.

Comparison groups	Core study period: MRX baseline values v Core study period: Week 48 values
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[31]
P-value	= 0.0307 [32]
Method	Student's t-test
Parameter estimate	Mean difference (net)
Point estimate	51.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.4
upper limit	97.7
Variability estimate	Standard deviation
Dispersion value	89.77

Notes:

[31] - The null hypothesis that the mean change was equal to zero was tested using the Student's t-test to determine if the mean change in ALT levels between MRX baseline and Week 48 was statistically significant.
[32] - Data for this analysis were obtained from 19 participants at MRX baseline; 17 of those participants contributed Week 48 data.

Secondary: Change from MRX baseline over time in alanine aminotransferase

End point title	Change from MRX baseline over time in alanine aminotransferase

End point description:

This secondary efficacy endpoint is the mean change from MRX baseline over time in ALT levels. The secondary objectives were defined as "up to and including Week 72" while the endpoints evaluated the change from baseline to Week 48. Results reported here are the long-term results, including Week 72 and subsequent visits.

End point type	Secondary

End point timeframe:

MRX baseline to EOT

End point values	Core study period: MRX baseline values	Week 252 values		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19[33]	6[34]		
Units: U/L				
arithmetic mean (standard deviation)	130.7 (± 59.12)	175.3 (± 101.17)		

Notes:

[33] - Data collected from 19 participants at MRX baseline.

[34] - Data collected at Week 252 from all 6 participants who contributed values at MRX baseline.

Statistical analyses

Statistical analysis title	Change from MRX baseline over time in ALT

Statistical analysis description:

This analysis investigated whether a statistically significant change in ALT levels was observed over time (with Week 252 chosen as the end point, as the last analysis visit with at least 6 participants). The analysis was based on the safety population.

Comparison groups	Core study period: MRX baseline values v Week 252 values
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	equivalence[35]
P-value	= 0.4934 [36]
Method	Student's t-test
Parameter estimate	Mean difference (net)
Point estimate	42.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-105
upper limit	189.7
Variability estimate	Standard deviation
Dispersion value	140.41

Notes:

[35] - The null hypothesis that the mean change was equal to zero was tested using the Student's t-test to determine if the mean change in ALT levels from baseline over time (to Week 252) was statistically significant.

[36] - Data for this analysis were obtained from 19 participants at MRX baseline; 6 of those participants contributed Week 252 data.

Secondary: Change from MRX baseline to Week 48 in aspartate aminotransferase

End point title	Change from MRX baseline to Week 48 in aspartate aminotransferase

End point description:

This secondary efficacy endpoint is the mean change from MRX baseline to Week 48 in AST levels. The secondary objectives were defined as "up to and including Week 72" while the endpoints evaluate the change from baseline to Week 48. Results reported here are for the Week 48 endpoint.

End point type	Secondary

End point timeframe:

MRX baseline to Week 48

End point values	Core study period: MRX baseline values	Core study period: Week 48 values		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19[37]	17[38]		
Units: U/L				
arithmetic mean (standard deviation)	127.6 (± 60.03)	142.4 (± 78.94)		

Notes:

[37] - Data collected from 19 participants at MRX baseline.

[38] - Data collected at Week 48 from 17 of the 19 participants who contributed values at MRX baseline.

Statistical analyses

Statistical analysis title	Change from MRX baseline to Week 48 in AST

Statistical analysis description:

This analysis investigated whether a statistically significant change in AST levels was observed when comparing MRX baseline to Week 48. The analysis was based on the safety population.

Comparison groups	Core study period: MRX baseline values v Core study period: Week 48 values
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[39]
P-value	= 0.1571 [40]
Method	Student's t-test
Parameter estimate	Mean difference (net)
Point estimate	21.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.1
upper limit	51.6
Variability estimate	Standard deviation
Dispersion value	58.98

Notes:

[39] - The null hypothesis that the mean change was equal to zero was tested using the Student's t-test to determine if the mean change in AST levels between MRX baseline and Week 48 was statistically significant.
[40] - Data for this analysis were obtained from 19 participants at MRX baseline; 17 of those participants contributed Week 48 data.

Secondary: Change from MRX baseline over time in aspartate aminotransferase

End point title	Change from MRX baseline over time in aspartate aminotransferase

End point description:

This secondary efficacy endpoint is the mean change from MRX baseline over time in AST levels. The secondary objectives were defined as "up to and including Week 72" while the endpoints evaluated the change from baseline to Week 48. Results reported here are the long-term results, including Week 72 and subsequent visits.

End point type	Secondary

End point timeframe:

MRX baseline to EOT

End point values	Core study period: MRX baseline values	Week 252 values		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19[41]	6[42]		
Units: U/L				
arithmetic mean (standard deviation)	127.6 (± 60.03)	145.0 (± 56.50)		

Notes:

[41] - Data collected from 19 participants at MRX baseline.

[42] - Data collected at Week 252 from 6 participants who contributed values at MRX baseline.

Statistical analyses

Statistical analysis title	Change from MRX baseline over time in AST

Statistical analysis description:

This analysis investigated whether a statistically significant change in AST levels was observed over time (with Week 252 chosen as the end point as the last analysis visit with at least 6 participants). The analysis was based on the safety population.

Comparison groups	Core study period: MRX baseline values v Week 252 values
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	equivalence[43]
P-value	= 0.7815 [44]
Method	Student's t-test
Parameter estimate	Mean difference (net)
Point estimate	12.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-94.7
upper limit	119
Variability estimate	Standard deviation
Dispersion value	101.84

Notes:

[43] - The null hypothesis that the mean change was equal to zero was tested using the Student’s t-test to determine if the mean change in AST levels from baseline over time (to Week 252) was statistically significant.

[44] - Data for this analysis were obtained from 19 participants at MRX baseline; 6 of those participants contributed Week 252 data.

Secondary: Change from MRX baseline to Week 48 in gamma glutamyltransferase

End point title	Change from MRX baseline to Week 48 in gamma glutamyltransferase

End point description:

This secondary efficacy endpoint is the mean change from MRX baseline to Week 48 in GGT. The secondary objectives were defined as “up to and including Week 72” while the endpoints evaluate the change from baseline to Week 48. Results reported here are for the Week 48 endpoint.

End point type	Secondary

End point timeframe:

MRX baseline to Week 48

End point values	Core study period: MRX baseline values	Core study period: Week 48 values		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19[45]	17[46]		
Units: U/L				
arithmetic mean (standard deviation)	476.9 (± 376.85)	440.5 (± 230.60)		

Notes:

[45] - Data collected from 19 participants at MRX baseline.

[46] - Data collected at Week 48 from 17 of the 19 participants who contributed values at MRX baseline.

Statistical analyses

Statistical analysis title	Change from MRX baseline to Week 48 in GGT

Statistical analysis description:

This analysis investigated whether a statistically significant change in GGT levels was observed when comparing MRX baseline to Week 48. The analysis was based on the safety population.

Comparison groups	Core study period: MRX baseline values v Core study period: Week 48 values
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[47]
P-value	= 0.9513 [48]
Method	Student's t-test
Parameter estimate	Mean difference (final values)
Point estimate	-3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-136.4
upper limit	128.7
Variability estimate	Standard deviation
Dispersion value	257.78

Notes:

[47] - The null hypothesis that the mean change was equal to zero was tested using the Student’s t-test to determine if the mean change in GGT levels between MRX baseline and Week 48 was statistically significant.

[48] - Data for this analysis were obtained from 19 participants at MRX baseline; 17 of those participants contributed Week 48 data.

Secondary: Change from MRX baseline over time in gamma glutamyltransferase

End point title	Change from MRX baseline over time in gamma glutamyltransferase

End point description:

This secondary efficacy endpoint is the mean change from MRX baseline over time in GGT. The secondary objectives were defined as “up to and including Week 72” while the endpoints evaluated the change from baseline to Week 48. Results reported here are the long-term results, including Week 72 and subsequent visits.

End point type	Secondary

End point timeframe:

MRX baseline to EOT

End point values	Core study period: MRX baseline values	Week 252 values		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19[49]	6[50]		
Units: U/L				
arithmetic mean (standard deviation)	476.9 (± 376.85)	377.5 (± 163.10)		

Notes:

[49] - Data collected from 19 participants at MRX baseline.

[50] - Data collected at Week 252 from 6 participants who contributed values at MRX baseline.

Statistical analyses

Statistical analysis title	Change from MRX baseline over time in GGT

Statistical analysis description:

This analysis investigated whether a statistically significant change in GGT levels was observed over time (with Week 252 chosen as the end point as the last analysis visit with at least 6 participants). The analysis was based on the safety population.

Comparison groups	Core study period: MRX baseline values v Week 252 values
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	equivalence[51]
P-value	= 0.7133 [52]
Method	Student’s t-test
Parameter estimate	Mean difference (net)
Point estimate	-56.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-431.2
upper limit	317.9
Variability estimate	Standard deviation
Dispersion value	356.88

Notes:

[51] - The null hypothesis that the mean change was equal to zero was tested using the Student’s t-test to determine if the mean change in GGT levels from baseline over time (to Week 252) was statistically significant.

[52] - Data for this analysis were obtained from 19 participants at MRX baseline; 6 of those participants contributed Week 252 data.

Secondary: Change from MRX baseline to Week 48 in total and direct bilirubin

End point title	Change from MRX baseline to Week 48 in total and direct bilirubin

End point description:

This secondary efficacy endpoint is the mean change from MRX baseline to Week 48 in total bilirubin and direct bilirubin. The secondary objectives were defined as “up to and including Week 72” while the endpoints evaluate the change from baseline to Week 48. Results reported here are for the Week 48 endpoint.

End point type	Secondary

End point timeframe:

MRX baseline to Week 48

End point values	Core study period: MRX baseline values	Core study period: Week 48 values		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19[53]	17[54]		
Units: mg/dL				
arithmetic mean (standard deviation)				
Total bilirubin	4.47 (± 4.837)	4.25 (± 5.384)		
Direct bilirubin	3.80 (± 3.858)	3.21 (± 3.656)		

Notes:

[53] - Data collected from 19 participants at MRX baseline.

[54] - Data collected at Week 48 from 17 of the 19 participants who contributed values at MRX baseline.

Statistical analyses

Statistical analysis title	Change from MRX baseline to W48 in tot. bilirubin

Statistical analysis description:

This analysis investigated whether a statistically significant change in total bilirubin levels was observed when comparing MRX baseline to Week 48. The analysis was based on the safety population.

Comparison groups	Core study period: MRX baseline values v Core study period: Week 48 values
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[55]
P-value	= 0.7839 [56]
Method	Student's t-test
Parameter estimate	Mean difference (net)
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.05
upper limit	1.37
Variability estimate	Standard deviation
Dispersion value	2.348

Notes:

[55] - The null hypothesis that the mean change was equal to zero was tested using the Student’s t-test to determine if the mean change in total bilirubin levels between MRX baseline and Week 48 was statistically significant.

[56] - Data for this analysis were obtained from 19 participants at MRX baseline; 17 of those participants contributed Week 48 data.

Statistical analysis title	Change from MRX baseline to W48 in dir. bilirubin

Statistical analysis description:

This analysis investigated whether a statistically significant change in direct bilirubin levels was observed when comparing MRX baseline to Week 48. The analysis was based on the safety population.

Comparison groups	Core study period: MRX baseline values v Core study period: Week 48 values
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[57]
P-value	= 0.5298 [58]
Method	Student's t-test
Parameter estimate	Mean difference (net)
Point estimate	-0.15

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.66
upper limit	0.35
Variability estimate	Standard deviation
Dispersion value	0.982

Notes:

[57] - The null hypothesis that the mean change was equal to zero was tested using the Student's t-test to determine if the mean change in direct bilirubin levels between MRX baseline and Week 48 was statistically significant.

[58] - Data for this analysis were obtained from 19 participants at MRX baseline; 17 of those participants contributed Week 48 data.

Secondary: Change from MRX baseline over time in total and direct bilirubin

End point title	Change from MRX baseline over time in total and direct bilirubin

End point description:

This secondary efficacy endpoint is the mean change from MRX baseline over time in total bilirubin and direct bilirubin. The secondary objectives were defined as "up to and including Week 72" while the endpoints evaluated the change from baseline to Week 48. Results reported here are the long-term results, including Week 72 and subsequent visits.

End point type	Secondary

End point timeframe:

MRX baseline to EOT

End point values	Core study period: MRX baseline values	Week 252 values		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19[59]	6[60]		
Units: mg/dL				
arithmetic mean (standard deviation)				
Total bilirubin	4.47 (± 4.837)	5.05 (± 6.449)		
Direct bilirubin	3.80 (± 3.858)	3.53 (± 3.727)		

Notes:

[59] - Data collected from 19 participants at MRX baseline.

[60] - Data collected at Week 252 from 6 participants who contributed values at MRX baseline.

Statistical analyses

Statistical analysis title	Change from MRX baseline in total bilirubin

Statistical analysis description:

This analysis investigated whether a statistically significant change in total bilirubin levels was observed over time (with Week 252 chosen as the end point as the last analysis visit with at least 6 participants). The analysis was based on the safety population.

Comparison groups	Core study period: MRX baseline values v Week 252 values

Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	equivalence[61]
P-value	= 0.8218 [62]
Method	Student's t-test
Parameter estimate	Mean difference (net)
Point estimate	-0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.31
upper limit	5.24
Variability estimate	Standard deviation
Dispersion value	5.505

Notes:

[61] - The null hypothesis that the mean change was equal to zero was tested using the Student's t-test to determine if the mean change in total bilirubin levels from baseline over time (to Week 252) was statistically significant.
[62] - Data for this analysis were obtained from 19 participants at MRX baseline; 6 of those participants contributed Week 252 data.

Statistical analysis title	Change from MRX baseline in direct bilirubin

Statistical analysis description:

This analysis investigated whether a statistically significant change in direct bilirubin levels was observed over time (with Week 252 chosen as the end point as the last analysis visit with at least 6 participants). The analysis was based on the safety population.

Comparison groups	Core study period: MRX baseline values v Week 252 values
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	equivalence[63]
P-value	= 0.5549 [64]
Method	Student's t-test
Parameter estimate	Mean difference (net)
Point estimate	-0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.62
upper limit	1.58
Variability estimate	Standard deviation
Dispersion value	2.001

Notes:

[63] - The null hypothesis that the mean change was equal to zero was tested using the Student's t-test to determine if the mean change in direct bilirubin levels from baseline over time (to Week 252) was statistically significant.
[64] - Data for this analysis were obtained from 19 participants at MRX baseline; 6 of those participants contributed Week 252 data.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events are AEs with a start date on or after the first dose of study drug and started prior to the last dose of study drug plus 14 days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Safety population

Reporting group description: -

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 19 (31.58%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal stoma output decreased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
International normalised ratio increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Forearm fracture			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post procedural haemorrhage			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Procedural haemorrhage			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pericardial effusion			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Right ventricular failure			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			

Medical device change			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Ear haemorrhage			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Fibrinous bronchitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			

Pathological fracture			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastrointestinal infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 19 (94.74%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Thrombosis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
General disorders and administration site conditions			

Chest pain subjects affected / exposed occurrences (all)	2 / 19 (10.53%) 2		
Fatigue subjects affected / exposed occurrences (all)	3 / 19 (15.79%) 4		
Feeling abnormal subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Feeling hot subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Influenza like illness subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Pyrexia subjects affected / exposed occurrences (all)	8 / 19 (42.11%) 15		
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	2 / 19 (10.53%) 3		
Reproductive system and breast disorders Amenorrhoea subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	10 / 19 (52.63%) 21		
Epistaxis subjects affected / exposed occurrences (all)	3 / 19 (15.79%) 16		
Fibrinous bronchitis subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 2		

Nasal congestion subjects affected / exposed occurrences (all)	2 / 19 (10.53%) 3		
Oropharyngeal pain subjects affected / exposed occurrences (all)	7 / 19 (36.84%) 18		
Pleural effusion subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Pulmonary hypertension subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Rhinorrhoea subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 3		
Sneezing subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Psychiatric disorders			
Breath holding subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 2		
Enuresis subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Restlessness subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Sleep disorder subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Product issues			
Device occlusion subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 2		
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Bilirubin urine present			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Blood bilirubin increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Blood parathyroid hormone increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Body temperature increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
International normalised ratio increased			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	6		
Intracardiac pressure increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Urobilinogen urine increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Vitamin D decreased			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Vitamin E decreased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Clavicle fracture			

subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Concussion				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Contusion				
subjects affected / exposed	3 / 19 (15.79%)			
occurrences (all)	3			
Drain site complication				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Fall				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Hand fracture				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Head injury				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Joint injury				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Limb crushing injury				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Limb injury				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Post procedural fever				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	2			
Procedural pain				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Scratch				

subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	4		
Skin abrasion			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Stoma site erythema			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Stoma site pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Stress fracture			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Vaccination complication			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Wound haemorrhage			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	10		
Nervous system disorders			
Disturbance in attention			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	6 / 19 (31.58%)		
occurrences (all)	13		
Lethargy			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	6		
Poor quality sleep			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		

Seizure subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Somnolence subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Taste disorder subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Lymphadenopathy subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	4 / 19 (21.05%) 5		
Ear pruritus subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Abdominal distension subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Abdominal pain subjects affected / exposed occurrences (all)	11 / 19 (57.89%) 40		
Abdominal pain upper subjects affected / exposed occurrences (all)	2 / 19 (10.53%) 3		
Abnormal faeces			

subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Chapped lips				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Constipation				
subjects affected / exposed	2 / 19 (10.53%)			
occurrences (all)	2			
Dental caries				
subjects affected / exposed	2 / 19 (10.53%)			
occurrences (all)	2			
Diarrhoea				
subjects affected / exposed	11 / 19 (57.89%)			
occurrences (all)	18			
Faeces discoloured				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	2			
Flatulence				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Frequent bowel movements				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Gingival bleeding				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Haematochezia				
subjects affected / exposed	2 / 19 (10.53%)			
occurrences (all)	2			
Inguinal hernia				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Lip haemorrhage				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Malabsorption				

subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Melaena			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Mouth haemorrhage			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Teething			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	5 / 19 (26.32%)		
occurrences (all)	7		
Hepatobiliary disorders			
Biliary tract disorder			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Hepatic lesion			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Jaundice			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Drug eruption			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Dry skin			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Eczema			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Rash			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Rash maculo-papular			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Skin discolouration			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Skin lesion			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Skin ulcer			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Xanthelasma			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Pollakiuria			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		

Urinary incontinence			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	5		
Back pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Bone metabolism disorder			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Bone pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	8		
Infections and infestations			
Clostridium difficile infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Ear infection			
subjects affected / exposed	5 / 19 (26.32%)		
occurrences (all)	9		
Epstein-Barr virus infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Gastrointestinal infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Hepatitis infectious mononucleosis			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Impetigo			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	8 / 19 (42.11%)		
occurrences (all)	36		
Oral herpes			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	4		
Otitis media			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Tonsillitis			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	8		
Upper respiratory tract infection			
subjects affected / exposed	11 / 19 (57.89%)		
occurrences (all)	28		
Varicella			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	3		
Viral upper respiratory tract infection			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	5		
Metabolism and nutrition disorders			
Vitamin D deficiency			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 November 2013	Protocol Amendment 1 Updates were made to add exclusion of participants with a history or presence of gallstones or kidney stones.
28 February 2014	Protocol Amendment 2 Updates were made to: - Lower eligibility age from 2 years of age to 12 months - Alter the number of participants planned for enrollment from 60 to 42 - Revise text to indicate that participants who weighed 10 kg or more would receive a 1.0 mL solution containing MRX or placebo. Participants who weighed less than 10 kg would receive a 0.5 mL solution containing MRX or placebo. The volume administered would not change during the course of the study - Correct maximum MRX dose - Add PedsQL for infants
17 September 2014	Protocol Amendment 3 Updates were made to: - Change treatment (duration) period to collect additional long-term safety data from 48 weeks to 76 weeks, including a 4-week follow-up. The treatment period was changed from 48 weeks to 72 weeks - Change stable dosing period from 36 weeks to 60 weeks and study duration to 76 weeks, including a 4-week follow-up - Add study visits at Weeks 60 and 72 - Change Study Termination (End of Study) from Week 48 to Week 72 - Add PedsQL evaluation at Week 72 - Add Caregiver Impression of Change evaluation at Week 72 - Change Study Termination from Week 48 to Week 72 - Change the number of participants planned for enrollment from 42 to 18 - Modify biochemical markers of cholestasis and liver disease to include deletion of ALP and modification of bilirubin (total and direct) to total bilirubin in secondary evaluations for the durability of the therapeutic effect as mean change from Baseline (Day 0) to Week 48 and the change from Week 12 to Week 48 - Change the number of study centers from 14 to 3 - Add drug level evaluations at Week 72
04 November 2015	Protocol Amendment 4 Updates were made to include a follow-up treatment period (after Week 72) that was intended to offer the opportunity to eligible participants treated in Study LUM001-303 to continue on treatment after Week 72 until the first of the following occurred: (i) up to 52 weeks of additional treatment (Week 124), or (ii) in the event that a new study opened to enrollment.

16 May 2017	Protocol Amendment 5 Updates were made to: - Allow continued participation in the long-term follow-up treatment, beyond what was previously described in Protocol Amendment 4 - Clarify that study treatment in the follow-up treatment period could continue until the first of the following occurred: (i) the participants were eligible to enter another MRX study; (ii) MRX was available commercially; or (iii) the sponsor stopped the program or development in this indication - Clarify that eligible participants who had previously discontinued from the study could re-enter and receive study treatment in the follow-up treatment period (after Week 124) - Add additional objectives for the long-term follow-up treatment period as follows: exploration of a BID dosing regimen and higher daily dosing of MRX, assessment of AFP levels, assessment of the palatability of the MRX formulation in all participants, obtain safety and efficacy data in participants treated long term on MRX - Align the contraceptive requirements with the Heads of Medicine Clinical Trials Facilitation Group Recommendations Related to Contraception and Pregnancy Testing
08 February 2019	Protocol Amendment 5.1 Updates were made to: - Change the sponsorship from Lumena Pharmaceuticals LLC to Mirum Pharmaceuticals, Inc. - Add drug compliance at Week 4 - Add Afternoon Dose Escalation eligibility assessment at Week 12 starting at Repeating Period 2 - Add Caregiver Global Therapeutic Benefit Questionnaire

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported