

**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) | EMA-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 occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 19 (5.26%) 0 / 1 0 / 0 | | |
| Infections and infestations | | | |
| Gastrointestinal infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 19 (5.26%) 0 / 1 0 / 0 | | |
| Lower respiratory tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 19 (5.26%) 0 / 2 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Dehydration subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 19 (5.26%) 0 / 1 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 occurrences (all) | 1 / 19 (5.26%) 1 | | |
| Hypotension subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | | |
| Thrombosis subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | | |
| General disorders and administration site conditions | | | |

| | | | |
|---|------------------|--|--|
| Chest pain | | | |
| subjects affected / exposed | 2 / 19 (10.53%) | | |
| occurrences (all) | 2 | | |
| Fatigue | | | |
| subjects affected / exposed | 3 / 19 (15.79%) | | |
| occurrences (all) | 4 | | |
| Feeling abnormal | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences (all) | 1 | | |
| Feeling hot | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences (all) | 1 | | |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences (all) | 1 | | |
| Pyrexia | | | |
| subjects affected / exposed | 8 / 19 (42.11%) | | |
| occurrences (all) | 15 | | |
| Immune system disorders | | | |
| Seasonal allergy | | | |
| subjects affected / exposed | 2 / 19 (10.53%) | | |
| occurrences (all) | 3 | | |
| Reproductive system and breast disorders | | | |
| Amenorrhoea | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences (all) | 1 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 10 / 19 (52.63%) | | |
| occurrences (all) | 21 | | |
| Epistaxis | | | |
| subjects affected / exposed | 3 / 19 (15.79%) | | |
| occurrences (all) | 16 | | |
| Fibrinous bronchitis | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences (all) | 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 occurrences (all) | 1 / 19 (5.26%) 1 | | |
| Bilirubin urine present subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | | |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | | |
| Blood parathyroid hormone increased subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | | |
| Body temperature increased subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | | |
| International normalised ratio increased subjects affected / exposed occurrences (all) | 3 / 19 (15.79%) 6 | | |
| Intracardiac pressure increased subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | | |
| Urobilinogen urine increased subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | | |
| Vitamin D decreased subjects affected / exposed occurrences (all) | 2 / 19 (10.53%) 2 | | |
| Vitamin E decreased subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | | |
| Injury, poisoning and procedural complications Anaemia postoperative subjects affected / exposed occurrences (all) Clavicle fracture | 1 / 19 (5.26%) 1 | | |

| | | | |
|-----------------------------|-----------------|--|--|
| 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 | 1 / 19 (5.26%) | | |
| occurrences (all) | 1 | | |
| Somnolence | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences (all) | 1 | | |
| Taste disorder | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences (all) | 1 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences (all) | 1 | | |
| Lymphadenopathy | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences (all) | 1 | | |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 4 / 19 (21.05%) | | |
| occurrences (all) | 5 | | |
| Ear pruritus | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences (all) | 1 | | |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences (all) | 1 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 11 / 19 (57.89%) | | |
| occurrences (all) | 40 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 2 / 19 (10.53%) | | |
| occurrences (all) | 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 occurrences (all) | 1 / 19 (5.26%) 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 2 / 19 (10.53%) 5 | | |
| Back pain subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 2 | | |
| Bone metabolism disorder subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | | |
| Bone pain subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 2 | | |
| Pain in extremity subjects affected / exposed occurrences (all) | 4 / 19 (21.05%) 8 | | |
| Infections and infestations | | | |
| Clostridium difficile infection subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | | |
| Ear infection subjects affected / exposed occurrences (all) | 5 / 19 (26.32%) 9 | | |
| Epstein-Barr virus infection subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | | |
| Gastroenteritis subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | | |
| Gastrointestinal infection subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 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: <ul style="list-style-type: none">- 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: <ul style="list-style-type: none">- 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 | <p>Protocol Amendment 5</p> <p>Updates were made to:</p> <ul style="list-style-type: none"> - 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 | <p>Protocol Amendment 5.1</p> <p>Updates were made to:</p> <ul style="list-style-type: none"> - 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