# SYNOPSIS

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| **Name of Sponsor/Company:** | Mirum Pharmaceuticals, Inc. |
| **Name of Study Intervention:** | Maralixibat (or maralixibat chloride; formerly LUM001) |
| **Study Title:** | **ICONIC Study**: Long-Term, Open-Label Study with a Double-Blind, Placebo-Controlled, Randomized Drug Withdrawal Period of LUM001, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), in Patients with Alagille Syndrome |
| **Study Number:** | LUM001-304 |
| **Study Phase:** | 2 |
| **PIP and/or PSP Number (if applicable):** | EMEA-001475-PIP02-13 |
| **Number of Study Center(s) and Countries:** | Multi-center study in 7 countries and 10 clinical sites. |
| **Publications (if any):** | None. |
| **Study Period:** | This interim clinical study report (CSR) reports all available data at the data cut-off on 01 December 2019, representing a period of approximately 6 years from the date the first participant was screened in March 2014. A final analysis of the data will be performed after all enrolled participants have completed their final (or early termination [ET]) study visit and a final CSR will be produced. |
| **Methodology:** | This was a randomized, placebo-controlled, drug-withdrawal study with a long-term open-label (OL) extension in children with Alagille syndrome (ALGS) designed to evaluate the safety and efficacy of maralixibat (maralixibat chloride or MRX). The study comprised an 18-week OL run-in period (OL phase), a 4-week randomized, double-blind, placebo-controlled drug-withdrawal period (randomized withdrawal phase; RWD), a 26-week stable-dosing period at doses up to 400 µg/kg/day (after randomized withdrawal phase; ARW), and an optional long-term treatment period (long-term extension phase; LTE). During the long-term treatment period, participants may have had their dose of maralixibat increased to a maximum of 800 µg/kg/day (400 µg/kg twice daily [BID]), based on efficacy of serum bile acid (sBA) levels and Itch Reported Outcome (Observer) (ItchRO[Obs]) score and safety assessments. Participants continued in the optional long-term follow-up treatment period until the first of the following occurred: 1) the participants were eligible to enter another maralixibat study, 2) maralixibat was available commercially, or 3) the sponsor stopped the program or development in this indication. At the time of the data cut for this report, the furthest analysis time point reached by any participants was Week 264. |
| **Number of Participants (Planned and Analyzed):** | It was planned to enroll a total of approximately 30 participants.<br>Screened 36 Enrolled 31 Screen Failure 5<br>Analyzed (Safety) 31 Analyzed (MITT) 15 Analyzed (ITT) 31 |

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| **Diagnosis and Main Criteria for Inclusion and Exclusion:** | Male and female participants between the ages of 12 months and 18 years, inclusive, meeting the following key criteria were eligible to participate in the study:<br>• A diagnosis of ALGS based on the diagnostic criteria.<br>• Evidence of cholestasis (one or more of the following):<br>  ○ Total sBA >3× upper limit of normal (ULN) for age.<br>  ○ Conjugated bilirubin >1 mg/dL.<br>  ○ Fat-soluble vitamin deficiency otherwise unexplainable.<br>  ○ Gamma-glutamyltransferase (GGT) >3× ULN for age.<br>  ○ Intractable pruritus explainable only by liver disease.<br>• Average daily score >2 on the Itch Reported Outcome (ItchRO™) questionnaire (0=none; 4=very severe pruritus) for 2 consecutive weeks in the screening period, prior to dosing.<br>• Absence of the following: chronic diarrhea requiring specific intravenous fluid or nutritional intervention; surgical disruption of the enterohepatic circulation; liver transplant, decompensated cirrhosis (alanine transaminase [ALT] >15× ULN, INR >1.5, albumin <3.0 g/dL; history or presence of clinically significant ascites; variceal hemorrhage, and/or encephalopathy); history or presence of other concomitant liver disease, or history or presence of any disease or condition known to interfere with the absorption, distribution, metabolism, or excretion of drugs, including bile salt metabolism in the intestine, history or presence of gallstones or kidney stones; known diagnosis of HIV infection; cancer except for in situ carcinoma, or cancers treated at least 5 years prior to screening with no evidence of recurrence; administration of bile acid or lipid-binding resins within 28 days prior to screening and throughout the trial; known hypersensitivity to maralixibat or any of its components; participants weighing over 50 kg at screening or any other conditions or abnormalities which, in the opinion of the investigator or medical monitor, may compromise the safety of the participant, or interfere with the participant participating in or completing the study.<br><u>Eligible participants for the initial 52-week optional long-term follow-up treatment period:</u><br>Participants were considered eligible for the 52-week optional follow-up treatment period if they had:<br>• Completed the protocol through the Week 48 visit with no safety concerns.<br>• Participants who had undergone a surgical disruption of the enterohepatic circulation were not eligible to enter into the follow-up treatment period.<br>• Participants who were discontinued for other reasons were considered for the 52-week optional follow-up treatment period on an individual basis. The decision was made by the investigator in consultation with the medical monitor. |
| **Study Interventions, Dose, Mode of Administration, and Batch Numbers:** | All participants received maralixibat up to 400 µg/kg/day or a maximum daily dose of 20 mg/day during the initial OL treatment period of the study. After completion of the 12-week stable-dosing period, participants were randomized 1:1 in a 4-week double-blind maralixibat withdrawal period to either placebo or remained on maralixibat. Participants then entered a 26-week long-term stable-dosing period and all participants received maralixibat up to 400 µg/kg/day. Participants were |

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| | considered for an initial 52-week optional long-term treatment period, if eligible, receiving up to 400 µg/kg/day or the highest tolerated dose below the 400 µg/kg/day dose. Participants were then considered for the second optional long-term follow-up treatment, if eligible, receiving up to 800 µg/kg/day (given as twice-daily doses of 400 µg/kg). Participants were dosed orally using the dosing dispenser provided. For once daily (QD) dosing, the required dose was delivered in 0.5 mL volume for participants who weighed less than 10 kg at screening and in 1.0 mL for participants who weighed 10 kg or more at screening. For BID dosing, the required dose was delivered in half the dosing volume: 0.25 mL BID for participants who weighed less than 10 kg and 0.50 mL BID for participants who weighed 10 kg or more. For participants weighing less than 10 kg at study entry, once a weight of 10 kg was reached while in the study, the participant was moved from 0.5 mL maximum daily dosing volume (0.25 mL BID) to 1.0 mL maximum daily dosing volume (0.50 mL BID). |
| **Duration of Study Intervention:** | For an individual participant, the duration of the study, including participant screening, treatment, and safety follow-up, was expected to be approximately 52 weeks. Participants who completed 48 weeks of treatment and were eligible to receive further treatment could continue in an initial 52-week optional long-term follow-up treatment period, after which eligible participants could continue study treatment beyond Week 52 until the first of the following occurred: 1) the participant was eligible to enter another maralixibat study, 2) maralixibat was available commercially, or 3) the sponsor stopped the program or development in this indication. |
| **Study Objectives:** | The objectives of this study (up to and including Week 48) were:<br>• To evaluate the long-term safety and tolerability of maralixibat in children with ALGS<br>• To evaluate the effect of maralixibat on sBA levels in children with ALGS<br>• To evaluate the effect of maralixibat on biochemical markers of cholestasis and liver disease in children with ALGS<br>• To evaluate the effect of maralixibat on pruritus in children with ALGS<br>• To evaluate the long-term effect of maralixibat in children with ALGS during 48 weeks of treatment<br>The objectives of the optional long-term follow-up treatment period (after Week 48) were:<br>• To offer eligible participants treated in Study LUM001-304 continued study treatment after Week 48 until the first of the following occurred: 1) the participant was eligible to enter another maralixibat study, 2) maralixibat was available commercially, or 3) the sponsor stopped the program or development in this indication<br>• To explore a BID dosing regimen and higher daily dosing of maralixibat<br>• To obtain safety and efficacy data in participants treated long-term with maralixibat, including genotyping characteristics<br>• To assess the level of alpha-fetoprotein (AFP), a marker of hepatocellular carcinoma<br>• To assess palatability of the maralixibat formulation |

**Study Endpoints**

Primary Efficacy Endpoint

The primary efficacy endpoint of this study was the mean change from Week 18 to Week 22 of fasting sBA levels in participants who previously responded to maralixibat treatment, as defined by a reduction in sBA ≥50% from baseline to Week 12 or Week 18 in the Modified Intent-to-Treat [MITT] Population.

Secondary Efficacy Endpoints

- The change from Week 18 to Week 22 in:
  - Alkaline phosphatase (ALP)
  - Alanine aminotransferase (ALT)
  - Total bilirubin
  - Direct bilirubin
  - Pruritus in subjects who previously responded to maralixibat treatment as measured by ItchRO (ItchRO[Obs] and ItchRO[Pt])
- The change from baseline to Week 18 in:
  - Fasting sBA levels
  - ALP
  - ALT
  - Total bilirubin
  - Direct bilirubin
  - Pruritus as measured by ItchRO (ItchRO[Obs] and ItchRO[Pt])

Additional Efficacy Endpoints

- Responder analysis at Weeks 18, 48, 60, 72, 84, 96, and 100 in:
  - Pruritus response rates as measured by ItchRO (ItchRO[Obs] and ItchRO[Pt])
  - Clinician scratch scale (CSS)
- Change from baseline to Weeks 18, 22, and 48, and then every 12 weeks in:
  - Pruritus as measured by ItchRO (ItchRO[Obs] and ItchRO[Pt])
  - Fasting sBA levels
  - ALP
  - ALT
  - Total bilirubin
  - Direct bilirubin
  - Other biochemical markers of cholestasis (total cholesterol, low-density lipoprotein cholesterol [LDL-C])
  - Bile acid synthesis (serum 7α-hydroxy-4-cholesten-3-one [7αC4])
- Change from baseline for Pediatric Quality of Life questionnaire (PedsQL) at Weeks 18, 22, 48, 60, 72, 84, 96, and 100 and change from Week 18 to Week 22
- Patient Impression of Change (PIC) at Weeks 18, 22, 48, 84, 96, and 100 and change from Week 18 to Week 22
- Caregiver Impression of Change (CIC) at Weeks 18, 22, 48, 84, 96, and 100 and change from Week 18 to Week 22
- Caregiver Global Therapeutic Benefit (CGTB) assessment at Weeks 18, 22, 48, 84, 96, and 100 and change from Week 18 to Week 22

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| | • Change from baseline (Day 0) to Week 48 in xanthomas, as measured by Clinician Xanthoma Scale score<br>• Change from baseline in body height and weight at Weeks 3, 6, 12, 18, 18/LOCF, 22, 28, 38, 48, 48/LOCF, 60, 72, 84, 96, 100/LOCF, BID Day 0, BID Week 4, BID Week 8, and each 12-week repeating period<br>• Palatability of the maralixibat formulation over time<br>• Plasma levels of maralixibat at baseline (pre-dose) and over time<br><u>Safety Endpoints</u><br>The safety and tolerability endpoints for this study included the following:<br>• Incidence of adverse events (AEs) including serious, related to maralixibat, that led to withdrawal, special interest AEs, along with AEs by severity and by relationship to study medication<br>• Change from baseline (Day 0) in clinical safety laboratory values at each clinic visit (if applicable)<br>• Change from Week 18 in clinical safety laboratory values at Week 22 (if applicable)<br>• Observed AFP values over time<br>• Change from baseline (Day 0) in physical examination findings and vital signs at each clinic visit<br>• Change from Week 18 in physical examination findings and vital signs at Week 22<br>• Concomitant medication usage |
| **Demography and Baseline Characteristics:** | Of the participants who enrolled in the study, 29 (93.5%) completed the OL phase. Thirteen and 16 in the maralixibat and placebo groups, respectively, completed the RWD phase; 28 (90.3%) completed the ARW phase, 23 (79.3%) opted to continue treatment under Protocol Amendment 3 in the LTE phase; and 14 (60.9%) remained on study at the time of this interim report.<br>In the overall study population (N=31), there were more males (61.3%) than females at baseline with similar proportions within the maralixibat (n=13) and placebo groups (n=16). The mean (SD) age in the overall study population was 5.4 (4.25) years (range: 1 to 15 years) and was similar between the maralixibat and placebo groups. The majority of the participants were from Australia and France (each 29.0% of the overall study population).<br>The mean time since the original diagnosis of ALGS was 66.2 months in the overall study population, with 64.5 months in the group assigned to maralixibat during the RWD phase (RWD maralixibat) and 73.2 months in the group assigned to placebo during the RWD phase (RWD placebo). In the overall study population, 25.8% of participants had a family history of ALGS (7.7% and 43.8% in the maralixibat and placebo group, respectively). All participants had the JAGGED1 mutation present. In the RWD maralixibat group, 30.8% had documented bile duct paucity, compared to75.0% in the RWD placebo group. The majority of participants in the overall study population (93.5%) had used previous anti-pruritic treatment, with a similar distribution in the maralixibat and placebo groups. The |

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| | most commonly reported anti-pruritic treatments used previously in the overall study population (reported by >50% of participants) included oral enzyme inducers (e.g., rifampicin) and oral ursodiol (ursodeoxycholic acid).<br><br>The baseline mean (SD) ItchRO(Obs) weekly morning average scores in the overall population were 2.909 (0.5480) (item 1; severity) and 3.001 (0.5992) (item 2; frequency) with similar scores in the maralixibat and placebo groups. The baseline CSS scores showed the majority of participants in the overall study population had evident abrasions (score 3; 32.3%) or evident cutaneous mutilation, hemorrhage, or scarring (score 4; 51.6%), with similar proportions in the RWD maralixibat and placebo groups. Just under half of participants had xanthomas (n=14), with most presenting as minimal (n=8).<br><br>Mean (SD) baseline ALT level in the overall study population was 181.0 (108.56) U/L, with a mean level of 217.8 (149.93) U/L in the RWD maralixibat group and 147.0 (54.60) U/L in the RWD placebo group. In the overall study population, the mean (SD) baseline total bilirubin level was 6.09 (5.781) mg/dL and mean direct bilirubin level was 4.57 (3.666) mg/dL, with similar values in the RWD maralixibat and placebo groups. Mean (SD) baseline 7αC4 levels were higher in the RWD maralixibat group (14.77 [19.874] ng/mL) than in the RWD placebo group (6.53 [8.728] ng/mL). |
| **Exposure:** | In the overall study population, the treatment duration (SD) was 944 (587.07) days, with a mean average daily dose (SD) of 439.8 (133.47) µg/kg/day. |
| **Efficacy Results:** | *Serum Bile Acids*<br><br>The primary efficacy endpoint was the change from Week 18 to Week 22 in fasting sBA levels in participants who had a reduction in sBA ≥50% from baseline to Week 12 or Week 18 (MITT Population). Fifteen participants (5 assigned to the maralixibat group; 10 assigned to the placebo group during the RWD phase) met this prespecified sBA reduction criterion.<br><br>Within this sBA responder subgroup, participants who were treated with placebo during the RWD phase had significant increases in sBA from Week 18 to Week 22 (LS mean [SE] increase of 95.55 [30.488] µmol/L, p-value = 0.0086), whereas those remaining on maralixibat had no notable change (LS mean [SE] decrease, or improvement of 21.73 [43.125] µmol/L, p-value = 0.6234), leading to a statistically significant difference in sBA between the maralixibat and placebo groups (-117.28 [52.828] µmol/L, p-value = 0.0464) using an ANCOVA model. Similar results were seen in the ITT Population in which the change in LS mean sBA from Week 18 to Week 22 differed significantly between the 2 treatment groups (p-value = 0.0254).<br><br>In the overall ITT Population, sBA was reduced significantly from baseline to Week 18 (mean change from baseline [SD] -87.73 [119.979] µmol/L, p-value = 0.0005), and from baseline to Week 48 (mean change from baseline [SD] -96.44 [166.631] µmol/L, p-value = 0.0058). Statistically significant mean decreases from baseline in sBA were observed at each time point, with the exception of Week 108 and Weeks ≥240.<br><br>*ItchRO(Obs): Weekly Average Morning Severity Score*<br><br>At Week 18, a statistically significant mean (SD) decrease (improvement) from baseline in ItchRO(Obs) weekly average morning severity scores was identified in the overall ITT Population (-1.704 [0.9114], p-value < 0.0001) with similar reductions observed in the maralixibat and placebo groups when analyzed |

separately. At Week 22, a statistically significant increase (worsening) in mean (SD) change from Week 18 in ItchRO(Obs) scores was observed in the placebo group (1.712 [1.0054], p-value < 0.0001), whereas no relevant change was observed in the maralixibat group (0.201 [0.7551]; p-value=0.3754). Using the ANCOVA model, the change in LS mean (SE) ItchRO(Obs) weekly average morning severity scores from Week 18 to Week 22 differed significantly between the maralixibat and placebo groups (-1.483 [0.3103]; p-value < 0.0001).

At Week 48, when all participants were administered maralixibat, a statistically significant mean (SD) decrease (improvement) from baseline was seen in ItchRO(Obs) weekly average morning severity scores (-1.620 [1.2999]; p-value <0.0001). For overall maralixibat (pooled maralixibat and placebo groups), statistically significant mean decreases from baseline in ItchRO(Obs) weekly average morning severity scores were observed at each analysis visit during the entire observation period up to Week 240 (with the exception of Week 132 which included data from only 5 patients), indicating improvement in pruritus.

*ItchRO(Obs): Weekly Average Score (Daily Maximum)*

In the overall ITT Population, mean (SD) baseline ItchRO(Obs) weekly average score (based on daily maximum of morning and evening severity scores) was 3.129 (0.4656). At Week 18, mean (SD) ItchRO(Obs) scores decreased (improved) to 1.382 (0.8938), resulting in a statistically significant mean change from baseline [SD] in ItchRO(Obs) (-1.736 [0.9559]; p-value < 0.0001) with similar reductions observed in the maralixibat and placebo groups when analyzed separately.

At Week 22, a statistically significant increase (worsening) in mean change [SD] from Week 18 in ItchRO(Obs) weekly average severity scores was identified in the placebo group (1.781 [1.0612]; p-value < 0.0001), whereas no difference from Week 18 in mean [SD] ItchRO(Obs) was observed in the maralixibat group (0.154 [0.7201]; p-value = 0.4560). The LS mean change in ItchRO(Obs) from Week 18 to 22 differed significantly between the 2 treatment groups in the ANCOVA model (p-value < 0.0001).

*ItchRO(Obs): Various Analysis Methods and Responder Analysis*

Consistently, statistically significant results were found in the changes in pruritus severity analyses performed on the ItchRO(Obs) from Week 18 to Week 22, based on the weekly average morning, weekly average evening severity score, 4-week average morning severity score, 4-week average evening severity score, and weekly average severity score (daily average of morning and evening scores) in the ITT Population, with use of an ANCOVA model. Sensitivity analyses conducted on ItchRO(Obs) differences between the maralixibat and placebo groups between Week 18 and Week 22 were statistically significant across various statistical methods, subgroups, missing data assumptions, and covariate adjustments.

A responder analysis was performed using responder definitions that were based on changes in weekly morning average ItchRO(Obs) of different thresholds. At the end of the RWD period at Week 22, there was a consistently higher proportion of responders in the maralixibat group compared with those in the placebo group. An ItchRO(Obs) responder rate of >70% was observed at Week 48, as measured by a clinically meaningful change from baseline of ≥1.0 point.

*ItchRO(Pt): Weekly Average Severity Score (Daily Maximum)*

In the overall ITT Population of 14 participants who qualified to complete the ItchRO(Pt), mean (SD) baseline ItchRO(Pt) weekly average severity score (based on daily maximum of morning and evening scores) were 3.020 (0.5926). At

Week 18, mean ItchRO(Pt) scores decreased (improved) to 0.939 (0.8134), a statistically significant mean change [SD] from baseline in ItchRO(Pt) (-2.082 [0.9554]; p-value < 0.0001) with similar reductions observed in the maralixibat and placebo groups when analyzed separately.

At Week 22, a statistically significant increase (worsening) in mean change [SD] from Week 18 in weekly average severity ItchRO(Pt) scores was identified in the placebo group (1.968 [1.2326]; p-value = 0.0014), whereas no difference from Week 18 in mean [SD] ItchRO(Pt) was observed in the maralixibat group (-0.143 [0.9636]; p-value = 0.7569). The LS mean change [SD] in ItchRO(Pt) from Week 18 to 22 differed significantly between the maralixibat and placebo groups in the ANCOVA model (-2.105 [0.4628]; p-value = 0.0008).

*ItchRO(Pt): Weekly Average Morning Severity Score*

At Week 18, a statistically significant mean [SD] decrease (improvement) from baseline in ItchRO(Pt) weekly average morning severity scores was identified in the overall ITT Population (-2.072 [0.9931]; p-value < 0.0001) with similar reductions observed in the maralixibat and placebo groups when analyzed separately. At Week 22, a statistically significant increase (worsening) in mean change [SD] from Week 18 in ItchRO(Pt) scores was identified in the placebo group (1.808 [1.1367]; p-value = 0.0014), whereas no difference from Week 18 was observed in the maralixibat group (-0.095 [1.0311]; p-value = 0.8465). The LS mean change [SD] in ItchRO(Pt) weekly morning average severity score from Week 18 to 22 was statistically significantly different between the maralixibat and placebo groups in the ANCOVA model (-1.988 [0.4641]; p-value = 0.0013). At Week 48, when all participants were administered maralixibat, a statistically significant mean [SD] decrease (improvement) from baseline in ItchRO(Pt) scores was observed (-2.254 [1.0118]; p-value < 0.0001).

*Clinician Scratch Scale*

Pruritus scores for the overall ITT Population at baseline as assessed by the investigator using the CSS were a mean (SD) of 3.3 (0.90). At Week 18, a statistically significant mean [SD] decrease (improvement) from baseline in CSS scores was identified in the overall population (-1.8 [1.53]; p-value < 0.0001). At Week 22, a statistically significant increase (worsening) in mean change [SD] from Week 18 in CSS scores was identified in the placebo group (1.6 [1.63]; p-value = 0.0016), whereas no difference from Week 18 in mean [SD] CSS was observed in the maralixibat group (0.4 [1.26]; p-value = 0.2930. The LS mean change in CSS score from Week 18 to 22 differed significantly between the maralixibat and placebo groups in the ANCOVA model (p-value = 0.0311). At Week 48, when all participants were administered maralixibat, a statistically significant mean [SD] decrease (improvement) from baseline in CSS scores was observed (-1.8 [1.29]; p-value < 0.0001). Statistically significant mean reductions from baseline in CSS were noted at all weeks in the overall study population from baseline to Week 240, indicating improvement in pruritus.

*Other Efficacy Endpoints*

Participants in the maralixibat group did not have statistically significantly different ALT levels compared with placebo from baseline to Week 22, or from Week 18 to Week 22. No statistically significant change from baseline in ALT level was noted to Week 132. For Weeks 144 and beyond, a statistically significant mean increase from baseline in ALT level was noted for all weeks (range of mean increases: 57.6 to 104.1; p-values <0.05), with the exception of Week 204 (p-value = 0.0622).

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| | In the overall ITT Population, mean (SD) baseline ALP level was 601.3 (274.77) U/L. No statistically significant mean change from baseline in ALP levels was noted at any week in the overall population from baseline to Week 252, with the exception of Week 38 and Week 48, both of which showed statistically significant decreases in ALP levels compared with baseline (p-value = 0.0364 and p-value = 0.0242, respectively).<br><br>In the overall ITT Population, mean (SD) baseline total bilirubin levels were 6.09 (5.781) mg/dL. Numerical reductions in mean total bilirubin were observed across most time points and statistically significant at Weeks 6, 108, 120 and 132. Mean (SD) baseline direct bilirubin level was 4.57 (3.666) mg/dL. At Week 18, mean (SD) direct bilirubin level decreased to 3.98 (3.369) mg/dL, a statistically significant mean change from baseline (mean change from baseline [SD] -0.5 [1.012] mg/dL, p-value = 0.0139).Overall, numerical reductions in mean direct bilirubin levels were observed across all time points, with statistically significant mean reductions from baseline noted for Weeks 18, 38, 72, 84, 100/LOCF, 108, 120, 132, 156 and 204.<br><br>In the overall study population, a statistically significant mean increase (improvement) from baseline in PedsQL Total Score (Parent) was noted at the majority of time points to Week 108 with the exception of Week 22 and Week 100/LOCF (range of mean significant increases: 8.10 – 15.65). After Week 108, the mean change from baseline in PedsQL Total Score (Parent) was not statistically significant, with the exception of Week 228 (p-value = 0.0406). A statistically significant increase (improvement) in change from baseline in PedsQL Multidimensional Fatigue Scale Score (Parent) was noted at all weeks in the overall study population to Week 228.<br><br>In the overall study population, while weight z-scores did not change significantly, there was an increase from baseline in mean height z-score at all time points after Week 3 to Week 252 (range of mean increase: 0.067 to 0.516) with statistically significant increases at Weeks 28, 38, 100/LOCF, 108, and 132 to 228.<br><br>The mean (SD) clinician xanthoma severity score at baseline was 0.9 (1.26) for the overall study population. At Week 48, a statistically significant mean decrease (improvement) from baseline was observed for the overall study population (mean [SD] 0.4 [0.69], p-value = 0.0095). |

**Safety Results:**

A summary of treatment-emergent adverse events (TEAEs) during the observation period is presented below.

| | OL Phase (Day 1 to Week 18) | RWD Phase (Weeks >18 to 22)[b] | | ARW Phase (Weeks > 22 to 48)[b] | LTE (Weeks > 48)[b] |
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| | MRX | MRX | Placebo | MRX | MRX |
| **Category** | **N=31 (%)** | **N=13 (%)** | **N=16 (%)** | **N=29 (%)** | **N=23 (%)** |
| Subjects with at least 1: | | | | | |
| TEAE | 30 (96.8) | 7 (53.8) | 12 (75.0) | 25 (86.2) | 23 (100.0) |
| TEAE potentially related to study drug[a] | 12 (38.7) | 1 (7.7) | 3 (18.8) | 1 (3.4) | 8 (34.8) |
| SAE | 4 (12.9) | 1 (7.7) | 1 (6.3) | 5 (17.2) | 6 (26.1) |
| SAE potentially related to study drug[a] | 0 | 0 | 0 | 0 | 0 |
| TEAE leading to study drug discontinuation | 2 (6.5) | 0 | 0 | 2 (6.9) | 2 (8.7) |
| TEAE leading to death | 0 | 0 | 0 | 0 | 0 |

AE = adverse event; ARW = after randomized withdrawal; LTE = long-term extension; MRX = maralixibat; OL = open-label; RWD = randomized withdrawal; SAE = serious adverse event; TEAE = treatment-emergent adverse event

a Any TEAE determined as possibly related or related, or is missing, is considered as potentially related to study drug.

b Subjects that terminated the study during the OL Phase are not included.

Note: Percentages are 100*n/N. Treatment groups are based on the dose received at the onset of the AE. TEAEs 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. For participants with >14 days of study drug interruption/withdrawal, the definition of a TEAE will consider both the date of the last dose before study drug interruption and the actual last dose. For these participants, AEs that start >14 days after the last dose before study drug interruption and end before the drug is re-administered will not be considered as treatment-emergent. AEs are counted only for the dose that the participant was taking during the start of the event.

The incidence of TEAEs was similar during the OL, the ARW and LTE phases, with the majority of participants (86.2-100%) experiencing TEAEs and 34.8-38.7% experiencing potentially-related TEAEs with only one case (3.4%) occurring between Week 22 and 48. During the RWD phase, participants that stayed on maralixibat had a lower incidence of TEAEs and potentially related TEAEs (53.8% and 7.7%, respectively) compared with participants on placebo (75% and 18.8%, respectively). During the RWD phase, SAEs were reported for 1 participant who stayed on maralixibat and 1 participant on placebo. None of the SAEs were considered related to study drug. A total of 6 participants experienced TEAEs leading to study drug discontinuation. No deaths occurred during the study.

*Frequency of TEAEs by Preferred Term*

The most frequently reported TEAEs (>30% in at least 1 phase) were abdominal pain; pyrexia; diarrhea; nasopharyngitis; vomiting; cough; and pruritus. The incidence of abdominal pain was highest in the OL and LTE phases (12 participants, 38.7% and 12 participants, 52.2%, respectively) and was lower in the ARW phase (6 participants, 20.7%). During the RWD phase, participants that stayed on maralixibat had a similar incidence of abdominal pain TEAEs compared with participants on placebo (1 participant, 7.7% and 1 participant, 6.3%,

respectively). The incidence of pyrexia was highest in the LTE phase (10 participants, 43.5%) and was lower in the OL and ARW phases (6 participants, 19.4% and 7 participants, 24.1%). During the RWD phase, participants that stayed on maralixibat had a lower incidence of pyrexia TEAEs compared with participants on placebo (0 participants and 2 participants, 12.5%, respectively). The incidence of diarrhea was highest in the OL and LTE phases (13 participants, 41.9% and 7 participants 30.4%, respectively) and was lower in the ARW phase (5 participants, 17.2%). During the RWD phase, participants that stayed on maralixibat had a similar incidence of diarrhea TEAEs compared with participants on placebo (1 participant, 7.7% and 1 participant, 6.3%, respectively). The incidence of nasopharyngitis was highest in the ARW and LTE phases (8 participants, 27.6% and 9 participants, 39.1%, respectively) and was lower in the OL phase (4 participants, 12.9%). During the RWD phase, participants that stayed on maralixibat had a similar incidence of nasopharyngitis TEAEs compared with participants on placebo (1 participant, 7.7% and 1 participant, 6.3%, respectively). The incidence of vomiting was highest in the OL and LTE phases (11 participants, 35.5% and 8 participants, 34.8%, respectively) and was lower in the ARW phase (3 participants, 10.3%). During the RWD phase, participants that stayed on maralixibat had a similar incidence of vomiting TEAEs compared with participants on placebo (1 participant, 7.7% and 1 participant, 6.3%, respectively). The incidence of cough was highest in the LTE phase (8 participants, 34.8%) and was lower in the OL and ARW phase (3 participants, 9.7% and 3 participants, 10.3%, respectively). During the RWD phase, no participants in either the RWD maralixibat or RWD placebo groups had a TEAE of cough. The incidence of pruritus was similar in the OLE, ARW, and LTE phases (3 participants, 9.7%, 2 participants, 6.9%, and 0 participants, respectively). During the RWD phase, participants that stayed on maralixibat had a lower incidence of pruritus TEAEs compared with participants on placebo (1 participant, 7.7% and 5 participants, 31.3%, respectively).

*Grade 3 and 4 TEAEs*

Most of the TEAEs reported during the study were mild or moderate in severity. The incidence of participants who experienced TEAEs of Grade 3 was similar during the OL and ARW phases (3 participants, 9.7% and 2 participants, 6.9%, respectively), and was higher during the LTE phase (5 participants, 21.7%), as would be expected from the longer exposure during the LTE phase. The Grade 3 TEAEs included the following: coagulopathy, abdominal pain, and pruritus (1 participant each, OL phase); abdominal pain, constipation, toxicity to various agents (verbatim term: voluntary paracetamol intoxication), blood bilirubin increased, and hypertension (1 participant each, ARW phase); and thrombocytopenia, cardiac dysfunction (verbatim term: worsening cardiac dysfunction), influenza-like illness, *Campylobacter* gastroenteritis, forearm fracture, ALT increased, and subclavian artery stenosis (1 participant each, LTE phase).

The incidence of Grade 4 TEAEs was similar during the OL and ARW phases (1 participant, 3.2% and 1 participant, 3.4%, respectively), and was higher during the LTE phase (3 participants, 13.0%), as would be expected from the longer exposure during the LTE phase. The Grade 4 TEAEs included the following: extradural hematoma and subdural hemorrhage (1 participant, OL phase); acute kidney injury (1 participant, ARW phase); and aplasia pure red cell, toxicity to various agents (verbatim term: voluntary rifadine intoxication), ALT increased, and marrow hyperplasia (1 participant each, LTE phase).

During the RWD phase, no participant that stayed on maralixibat had a Grade 3 or 4 TEAE, whereas 1 participant on placebo had Grade 3 TEAEs of hypertension and multiple injuries and a Grade 4 TEAE of shock hemorrhagic and splenic rupture, all of which were assessed as not related to study drug.

*Treatment-related AEs*

The incidence of participants who experienced treatment-related TEAEs was similar during the OL and LTE phases (12 participants, 38.7% and 8 participants, 34.8%, respectively), and was lower during the ARW phase (1 participant, 3.4%). Each of the treatment-related TEAEs reported during the OL phase occurred at a higher incidence during the OL phase compared with the LTE phase (abdominal pain, 9 participants [29.0%] and 4 participants [17.4%], respectively; diarrhea, 6 participants [19.4%] and 1 participant [4.3%], respectively; and vomiting, 3 participants [9.7%] and 0 participants [0%], respectively). Only 1 participant had a treatment-related TEAE (diarrhea) during the ARW phase. Treatment-related TEAEs of ALT increased (4 participants, 17.4%) and AST increased (2 participants, 8.7%) were reported only during the LTE phase. During the RWD phase, participants that stayed on maralixibat had a lower incidence of treatment-related TEAEs compared with participants on placebo (1 participant, 7.7% and 3 participants, 18.8%, respectively). All treatment-related TEAEs reported during the RWD phase were pruritus.

*Serious AEs*

In total, 14 participants experienced a total of 33 SAEs. None of the SAEs were considered by the investigator to be related to study drug. Infections and infestations (reported by 7 participants) and GI events (reported by 3 participants) were the most frequently reported types of SAEs. The incidence of SAEs was similar during the OL and ARW phases (4 participants, 12.9% and 5 participants, 17.2%, respectively) and was slightly higher during the LTE phase (6 participants, 26.1%), as would be expected from the longer exposure. During the RWD phase, participants that stayed on maralixibat had a similar incidence of SAEs compared with participants on placebo (1 participant, 7.7% and 1 participant, 6.3%, respectively).

*AEs leading to discontinuation*

A total of 6 participants experienced TEAEs leading to study drug discontinuation including extradural hematoma and subdural hemorrhage, both of which were Grade 4 in severity and considered by the investigator to be unlikely/remotely related to the study drug (Day 37); staphylococcal infection of moderate intensity that was considered by the investigator to be possibly related to the study drug (Day 6); acute kidney injury that was Grade 4 in severity and considered by the investigator to be not related to study drug (Day 336); blood bilirubin increased of severe intensity that was considered by the investigator to be not related to study drug (Day 197); ALT of severe intensity that was considered by the investigator to be related to the drug (Day 1386); and ALT increased of moderate intensity that was considered to be possibly related to study drug (Day 596).

*AEs of Special Interest*

Adverse events of special interest included diarrhea, fat-soluble vitamin deficiency, elevated transaminases and elevated bilirubin. The majority of TEAEs of diarrhea were mild to moderate in intensity and considered by the investigator as not related or unrelated to study drug. Three participants experienced 4 SAEs of diarrhea, one of which were assessed as related to study drug. The majority of all TEAEs

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| | associated with fat-soluble vitamin deficiency were considered mild or moderate in intensity. One participant (Participant 090001) experienced an SAE of a seizure of moderate intensity that was considered by the investigator to be not related to study drug and recovered/resolved without a dose change. One participant experienced 2 fat-soluble vitamin deficiency TEAEs that were considered possibly related to study drug (moderate epistaxis that recovered/resolved and mild visual acuity reduced that was not recovered/resolved). All other TEAEs associated with fat-soluble vitamin deficiency were considered unrelated or not related to study drug. The majority of all TEAEs associated with fat-soluble vitamin deficiency were considered mild or moderate in intensity. Treatment-emergent AEs associated with elevated transaminases were only reported during the LTE phase (4 participants, 17.4%). Four participants (17.4%) had TEAEs of ALT increased; of these 4 participants, 2 (8.7%) also had TEAEs of AST increased. No participant experienced an SAE associated with elevated transaminases. A single TEAE associated with elevated bilirubin was reported during the ARW phase (1 participant, 3.4%). Participant 040002 experienced a severe SAE of blood bilirubin increased that was considered by the investigator to be not related to study drug, was ongoing, and resulted in drug withdrawal. |
| **Conclusions:** | In Study LUM001-304, treatment with maralixibat resulted in reductions in sBA and control of pruritus. Treatment for a period of 18 weeks demonstrated clinically and statistically significant improvement in sBA and pruritus, as measured by weekly ItchRO scores. During the 4-week RWD phase, this improvement was maintained for those participants who continued with maralixibat treatment, whereas those participants who were randomized to placebo had significant worsening of sBA and pruritus, with levels increasing close to those observed at baseline. After the RWD period, when all participants again received maralixibat, both groups had sustained improvement in sBA levels and ItchRO scores over the long-term treatment duration.<br><br>The pruritus improvements were statistically significant across multiple measures (weekly average, weekly morning, weekly evening, 4-weekly and CSS) as assessed by caregivers, patients and investigators, and across multiple sensitivity and subgroup analyses. An ItchRO(Obs) responder rate of >70% was observed at Week 48, as measured by a clinically meaningful change from baseline of ≥1.0 point.<br><br>No statistically significant change from baseline in ALT level was noted until Weeks 144 and beyond when a statistically significant mean increase from baseline was noted. Reductions in mean total bilirubin were observed across most time points, reaching statistical significance at 4 time points. Numerical decreases in mean direct bilirubin levels were observed during the study, reaching statistical significance at many time points. No significant differences in ALT, total bilirubin, and direct bilirubin levels were noted between the maralixibat and placebo groups during the 4-week RWD period.<br><br>Overall, there was a statistically significant improvement from baseline in quality of life, as measured by the PedsQL Total Score (Parent) and the Multidimensional Fatigue Scale Score (Parent) noted at the majority of time points.<br><br>Participants in this study experienced a growth benefit, as demonstrated by statistically significant improvements in height z-score over time. Statistically significant improvements in weight z-scores were not observed.<br><br>A statistically significant improvement in xanthomas score was observed at Week 48. |

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| | In Study LUM001-304, maralixibat was safe and well tolerated. There were no deaths in Study LUM001-304.<br><br>Fourteen participants had a total of 33 SAEs. None of the SAEs were considered by the investigator to be related to study treatment.<br><br>The incidence of TEAEs and treatment-related AEs was similar during the OL and ARW phases after the RWD phase. During the RWD phase, participants who stayed on maralixibat had a lower incidence of TEAEs and treatment-related TEAEs compared with participants on placebo. A total of 6 participants had TEAEs that led to permanent treatment discontinuation. Gastrointestinal events (abdominal pain, diarrhea, and vomiting) were the most frequently reported related TEAEs, followed by increased ALT and AST, and pruritus. Apart from the TEAEs that led to permanent treatment discontinuation, most reported TEAEs were generally mild or moderate in severity.<br><br>The incidence of participants who experienced Grade 3 and 4 TEAEs was similar during the OL and ARW phases, and was higher during the LTE phase, as would be expected from the longer exposure during the LTE phase. During the RWD phase, no participant that stayed on maralixibat had a Grade 3 or 4 TEAE, whereas 1 participant on placebo had Grade 3 TEAEs of hypertension and multiple injuries and a Grade 4 TEAE of shock hemorrhagic and splenic rupture. Overall, Grade 4 TEAEs included aplasia pure red cell, extradural hematoma, subdural hemorrhage, splenic rupture, toxicity to various agents, increased ALT, acute kidney injury, marrow hyperplasia, and shock hemorrhagic.<br><br>Treatment-emergent events of diarrhea (diarrhea and gastroenteritis) were the most common TEAEs of special interest, followed by fat-soluble vitamin deficiency, elevated transaminases, and elevated bilirubin.<br><br>Overall, maralixibat demonstrated durable and clinically meaningful reduction in pruritus and control of sBA with associated improvements in growth, liver parameters, xanthoma scores, and quality of life. Maralixibat was shown to be well tolerated and demonstrated an acceptable long-term safety profile. |
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