SYNOPSIS

Name of Sponsor/Company:	Mirum Pharmaceuticals, Inc.
Name of Study Drug:	Maralixibat chloride (formerly LUM001)
Study Title:	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
Study Number:	LUM001-303
Study Phase:	2
PIP and/or PSP Number (if applicable):	EMEA-001475-PIP02-13
Number of Study Center(s) and Countries:	Multicenter study in 3 clinical sites in the United Kingdom that participated in study LUM001-302.
Publications (if any):	None
Study Period:	17 October 2013 to 01 December 2019 (interim cut-off date) This interim clinical study report (CSR) reports all available information at the data cut-off on 01 December 2019, representing a period of approximately 6 years from the date the first participant was enrolled in October 2013. 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 multicenter, double-blind study of maralixibat in children ≥12 months of age diagnosed with Alagille syndrome (ALGS) who completed participation in the LUM001-302 study. In Study LUM001-302, participants were randomized to receive either placebo or active drug (maralixibat). All participants received active drug (maralixibat) in Study LUM001-303. The study was divided into 5 parts: 1) a dose-escalation period, 2) a dose-optimization period, 3) a stable dosing period, 4) a 52-week follow-up treatment period, and 5) a long-term follow-up treatment period for eligible participants who chose to stay on treatment with maralixibat. <u>Dose-Escalation Period</u> All participants entering the extension study participated in a 4-week double-blind dose-escalation period during which: • Participants who were randomized to receive placebo during the LUM001-302 study received weekly dose increases of maralixibat up to a target dose of 140 µg/kg/day or to a maximum tolerated dose below 140 µg/kg/day (10 mg maximum total dose).

- Participants who were randomized to receive active drug during the LUM001-302 study continued to receive the dose of maralixibat that they were taking at Week 13 of the LUM001-302 study. The maralixibat doses for these participants remained blinded and were not altered during the dose-escalation period.

A minimum of 7 days was required to elapse between dose increases.

Dose-Optimization Period

After completion of the 4-week dose-escalation period, participants entered an 8-week dose-optimization period. During this period, the investigator had the option to adjust maralixibat dosing with the objective of achieving optimal control of pruritus at a dose level that was tolerated by the participant and up to a maximum daily dose of 280 µg/kg maralixibat or 20 mg total dose. The maralixibat dose level was increased or decreased in a double-blind manner. Increases in dose were based on efficacy (sBA and itch reported outcome observer ItchRO[Obs] score) and safety assessment results. Reductions in dose were based on tolerability. At the investigator's discretion, the doses for participants who were previously reduced could be re-challenged during the dose-optimization period. Each participant received one of the following dose levels:

- Maralixibat 35 µg/kg/day
- Maralixibat 70 µg/kg/day
- Maralixibat 140 µg/kg/day
- Maralixibat 280 µg/kg/day

A minimum of 7 days was required to elapse between dose increases.

Stable Dosing Period

After completion of the 8-week dose-optimization period, all participants entered the stable dosing period, which lasted 60 weeks. During the remainder of the study, participants were dosed with the Week 12 dose, or the highest tolerated dose below the Week 12 dose. However, if a participant experienced intolerance due to gastrointestinal symptoms, the investigator, in consultation with the medical monitor, could lower the dose to a previously tolerated dose.

Follow-up Treatment Period

At Week 72, all 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 maralixibat at the dose they were receiving at Week 72.

- For participants who were eligible to roll over into the follow-up treatment period, those with <7 days since the last dose of maralixibat, were maintained at the same dose level.
- For participants who were eligible to roll over into the follow-up treatment period having ≥7 days since the last dose of maralixibat, were dose escalated up to 280 µg/kg/day or the highest tolerated dose following a 4 week dose escalation beginning at 35 µg/kg/day.

	• For participants who did not wish to enter the follow-up treatment period, or 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 maralixibat. Long-term Follow-Up Treatment Period (Protocol Amendment 5) The long-term follow-up treatment period was for eligible participants who chose to stay on treatment with maralixibat. During this long-term follow-up treatment period, participants could have their dose of maralixibat increased to a maximum of 560 µg/kg/day (280 µg/kg twice daily [BID]), based on efficacy (sBA and ItchRO score) and safety assessment results. Participation in the long-term follow-up treatment period was to continue until the first of the following occurred: i) the participants were eligible to enter another maralixibat study, (ii) maralixibat was available commercially, or (iii) the sponsor stopped the program or development in this indication.
Number of Participants (Planned and Analyzed):	Approximately 18 participants who enrolled in the LUM001-302 study and who met the study's inclusion and exclusion criteria were planned for enrollment. LUM001-302 enrolled 20 participants, and 1 placebo participant did not enter LUM001-303. Screened 19 Enrolled 19 Screen Failure 0 Analyzed (Safety) 19
Diagnosis and Main Criteria for Inclusion and Exclusion:	Male and female participants between the ages of 12 months and 18 years, inclusive, who completed participation in study LUM001-302 were eligible to participate in the study. Participants must not have experienced an adverse event (AE) or serious adverse event (SAE) related to the study drug during study LUM001-302 that led to the discontinuation from the study. Participants with a history or presence of gallstones or kidney stones; or with a history of non-adherence during the LUM001-302 study were not eligible to participate. Eligible participants for the 52-week follow-up treatment period Participants were considered eligible for the 52-week follow-up treatment period if they completed the protocol through the Week 72 visit with no safety concerns. Eligible participants for the long-term follow-up treatment period Participants were considered eligible for the long-term follow-up treatment period if they completed the protocol through either the Week 124 or the Early Termination visit with no major safety concerns or discontinued due to safety reasons judged unrelated to the maralixibat, and laboratory results returned to acceptable levels. At the time of entry into the follow-up period, participants must not have met any of the protocol's stopping rules to be eligible.
Study Drugs, Dose, and Mode of Administration:	Oral maralixibat doses: 35, 70, 140, 280 µg/kg/day, and 280 µg/kg BID (560 µg/kg/day) Participants received a grape-flavored solution containing maralixibat, administered orally QD or BID using the dosing dispenser provided. The first dose was to be taken at least 30 minutes before the first meal of the day and the second dose, where applicable, was to be taken at least 30 minutes before dinner (main evening meal).

Duration of Study Drug:	For an individual participant, the study participation period consisted of a 4-week dose-escalation period, an 8-week dose-optimization period, a 60-week stable dosing period, a 52-week follow-up treatment period, and a long-term follow-up treatment period. A safety follow-up phone call was made by the study site 30 days after the last dose of maralixibat.
Study Objectives	Primary (up to and including Week 72) Evaluate the long-term safety and tolerability of maralixibat in pediatric participants with ALGS. Secondary (up to and including Week 72) • Evaluate the long-term effect of maralixibat on serum bile acid (sBA). • Evaluate the long-term effect of maralixibat on pruritus. • Explore the long-term effect of maralixibat on other biochemical markers of cholestasis and liver disease. • Evaluate the long-term effect of maralixibat on xanthomas. • Explore an expanded dosing range to identify the doses necessary to achieve the optimal benefit-to-risk ratio for this patient population. Long-Term Follow-Up Treatment Period • To offer eligible participants in the LUM001-303 study continued study treatment until the first of the following occur: (i) the participants are eligible to enter another maralixibat study, or (ii) maralixibat is available commercially, or (iii) the sponsor stops the program or development in this indication. • To explore twice a day (BID) dosing regimen and higher daily dosing of maralixibat. • To obtain safety and efficacy data in participants treated long term on maralixibat. • To assess the level of alpha-fetoprotein (AFP), a marker of hepatocellular carcinoma. • To assess palatability of the maralixibat formulation.
Study Endpoints	Primary Efficacy Endpoint Mean change from maralixibat baseline to Week 48 in fasting serum bile acid level Secondary Efficacy Endpoints • Mean change from maralixibat baseline to Week 48 in the following: • Biochemical markers of cholestasis and liver disease (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], gamma-glutamyltransferase [GGT], and total and direct bilirubin] • Pruritus as measured by the caregiver, itch reported outcome instrument (ItchRO[Obs]^{TM})

- Xanthomas as measured by clinician xanthoma scale

Safety Endpoints

- AEs and SAEs
- Clinical laboratory results
- Vital signs
- Physical examination findings, including body weight and height
- Concomitant medication usage
- AFP

Summary of Results and Conclusions:

Demography and Baseline Characteristics:

A total of 19 participants were enrolled and treated in the core study (Day 1 to Week 72), with 5 of these participants assigned placebo in LUM001-302 (PBO-MRX group) and 14 of these participants assigned to any dose level of maralixibat in LUM001-302 (MRX-MRX group).

In the overall population, 9 females (47.4%) and 10 males (52.6%) were enrolled in the study. More females (4 [80.0%]) than males (1 [20.0%]) were enrolled in the PBO-MRX group and more males (9 [64.3%]) than females (5 [35.7%]) were enrolled in the MRX-MRX group. In the overall population, the mean (SD) age at maralixibat baseline was 6.0 (5.02) years, and participants ranged from 1 to 16 years of age. Most participants were white (16 [84.2%]) and between 2 to 4 years of age (6 [31.6%]) or 5 to 8 years of age (5 [26.3%]). There were approximately 3 times as many participants in the MRX-MRX group (N=14) than in the PBO-MRX group (N=5), since Study LUM001-302 had 2 active treatment groups (140 µg/kg/day and 280 µg/kg/day) and a placebo group, designed to allocate 6 participants to each of the maralixibat dose groups and 6 participants to the placebo group.

In the overall population, the mean (SD) time from the original diagnosis of ALGS to the first dose of maralixibat was 67.6 (61.90) months, with a range of 12 to 200 months. In the overall population, most participants (14 [73.7%]) had no family history of ALGS. A total of 9 participants (47.4%) had bile duct paucity at baseline. Most participants (18 [94.7%]) had JAGGED1 mutation, none had NOTCH2 mutation, and a mutation was not identified for 1 participant (5.3%). Most participants (16 [84.2%]) previously used anti-pruritic treatments. All participants had additional clinical features of ALGS, with the most frequent being chronic cholestasis and characteristic facial features (100%), vascular abnormalities (68.4%), cardiac disease (63.2%), and skeletal abnormalities (57.9%).

Exposure:

In the overall study population, the median duration of maralixibat exposure was 516 days.

Efficacy Results:

Note that primary and secondary objectives were defined as “up to and including Week 72” while the endpoints evaluate the change from baseline to Week 48. This interim report includes the results for the Week 48 endpoint as well as the long-term results including Week 72 and subsequent visits. For participants who were assigned maralixibat 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 maralixibat baseline values were used and defined as the values on the day maralixibat treatment started in either Study LUM001-303 (for the PBO-MRX group) or Study LUM001-302 (for the MRX-MRX group), where appropriate. Missing data due to treatment interruptions experienced for operational reasons between protocol amendments should be taken into account when interpreting results between Week 72 and Week 124.

Serum Bile Acids

In the overall population, a statistically significant reduction (improvement) in sBA concentrations (mean [SD] change from maralixibat baseline to Week 48 (-94.40 [98.915] µmol/L; p=0.0012) was observed. A statistically significant reduction (improvement) in sBA concentrations was observed for the MRX-MRX group (mean [SD] change from maralixibat baseline to Week 48, -107.24 [110.119] µmol/L; p=0.0062) whereas the change from maralixibat baseline to Week 48 in the PBO-MRX group (N=5) was not significant (-63.61 [64.110] µmol/L; p=0.0908). The reduction (improvement) in mean change from maralixibat baseline in sBA was statistically significant ($p \leq 0.05$) in the overall population at Weeks 4 through 60, Weeks 132 through 156, and Weeks 192 through 252.

ItchRO(Obs)

In the overall population, the baseline mean (SD) ItchRO(Obs) weekly average morning severity score was 2.435 (0.7952). At Week 48, a statistically significant mean (SD) decrease (improvement) from maralixibat baseline in ItchRO(Obs) weekly average morning severity score (-1.095 [0.7173]; p<0.0001) was observed in the overall population. Statistically significant mean decreases (improvements) in ItchRO(Obs) weekly average morning severity score from maralixibat baseline were also observed for the PBO-MRX and MRX-MRX groups (mean [SD] -1.679 [0.4805], p=0.0014 and -0.852 [0.6672], p=0.0010; respectively).

Biochemical Markers of Cholestasis and Liver Disease Biochemical Markers

At Week 48, a mean (SD) increase in ALP levels from maralixibat baseline of 7.4 (210.32) U/L was observed in the overall population.

At Week 48, a statistically significant mean (SD) increase from maralixibat baseline in ALT of 51.6 (89.77) U/L was observed (p=0.0307) in the overall population. Statistically significant mean changes from maralixibat baseline in ALT were also observed at Weeks 24 (p=0.0286) and 36 (p=0.0280).

At Week 48, a mean (SD) increase from maralixibat baseline in AST of 21.2 (58.98) U/L was observed.

At Week 48, a mean (SD) decrease in GGT levels from maralixibat baseline of -3.9 (257.78) U/L was observed in the overall population. Mean change from maralixibat baseline in GGT was statistically significant at Week 72 only (107.3 [148.90] U/L, p=0.0380).

At Week 48, a mean (SD) change from maralixibat baseline in total bilirubin of 0.16 (2.348) mg/dL was observed in the overall population. The mean change from maralixibat baseline in total bilirubin was statistically significant at Week 8 only (-0.74 [1.320] mg/dL, p=0.0296).

At Week 48, a mean (SD) change from maralixibat baseline in direct bilirubin of -0.15 (0.982) mg/dL was observed in the overall population. The mean change from maralixibat baseline in direct bilirubin was statistically significant at Week 8 only (-0.36 [0.655] mg/dL, p=0.0343).

In the overall population, the only statistically significant mean (SD) change from maralixibat baseline in C4 was observed at Week 48 (15.01 [25.731] ng/mL, p=0.0340).

Clinician Xanthoma Severity Score

In the overall population, the mean clinician xanthoma severity score (SD) at baseline was 0.4 (0.55) based on the PBO-MRX group because there was no maralixibat baseline xanthoma score for the MRX-MRX group as it was not assessed in Study LUM001-302. Over the duration of the study, the mean xanthoma severity score ranged from 0.0 (Week 60) to 0.6 (Week 144).

Other Efficacy Endpoints

Height, Weight, and BMI z-Scores

Over the study duration, increases (improvements) from maralixibat baseline in height z-scores were observed at all visits in the overall population (range: 0.008 [Week 2] to 0.568 [Week 252]). Statistically significant ($p \leq 0.05$) mean increases from maralixibat baseline in height z-scores were observed at Weeks 36, 48, and 60.

Over the study duration, increases (improvements) from maralixibat baseline in weight z-scores were observed at all visits (range: 0.007 [Week 36] to 0.698 [Week 252]) with the exception of 1 mean (SD) decrease from maralixibat baseline at Week 4 (0.002 [0.3066]) in the overall population; none were statistically significant.

Over the study duration, decreases from maralixibat baseline in BMI (kg/m^2) z-scores were observed from Week 12 to Week 156 and at Week 240 (range: -0.007 [Week 240] to -0.203 [Week 144]) with varying mean increases (improvements) from maralixibat baseline observed at all other visits (range: 0.021 [Week 228] to 0.271 [Week 252]) in the overall population; none were statistically significant.

Lipids

In the overall population, the only statistically significant mean (SD) change from maralixibat baseline in total cholesterol was observed at Week 48 (-27.1 [34.19] mg/dL, p=0.0082).

In the overall population, the only statistically significant mean (SD) decrease from maralixibat baseline in LDL-C was observed at Week 216 (-29.6 [16.29] mg/dL, p=0.0153).

Clinician Scratch Scale Score

In the overall population, at Week 48, a statistically significant mean (SD) decrease from maralixibat baseline in CSS was observed (-0.7 [0.99], p=0.0093). Statistically significant ($p \leq 0.05$) mean (SD) decreases from maralixibat baseline in CSS were observed at most visits throughout the study (mean change from maralixibat baseline ranged from -0.6 [Week 60] to -2.0 [Week 216]).

Caregiver Impression of Change – Xanthoma Severity

In the overall population, the mean CIC – xanthoma severity was ≤3.7 at Weeks 48 and 72.

Pediatric Quality of Life Evaluation

In the overall study population, statistically significant (p-value ≤0.05) mean increases (improvements) from maralixibat baseline were observed as follows:

- PedsQL Total Scale Score (Parent) at Week 24 (p= 0.0217), Week 48 (p=0.0018), and Week 72 (p=0.0386)
- PedsQL Multidimensional Fatigue Scale Score (Parent) and in PedsQL Psychosocial Health Summary Score (Parent) at Week 48 (mean [SD] change from maralixibat baseline: 13.00 [17.327], p=0.0148 and 11.61 [14.472], p=0.0059, respectively)
- PedsQL Family Impact Total Scale Score were observed at Week 24 (9.34 [12.349], p=0.0085), Week 48 (11.19 [12.020], p=0.0014), and Week 72 (12.66 [13.894], p=0.0047)

Safety Results:

In a post-hoc analysis of treatment duration by dose level in the Safety Population, the mean (SD) treatment duration for the overall study population was 811.1 (569.31) days. Participants were on a high dose of maralixibat for a longer period of time.

In the overall population, 18 participants (94.7%) had at least 1 TEAE and 15 (78.9%) had at least 1 AE that was related to study drug. In the overall population, 6 participants (31.6%) had at least 1 SAE and 1 participant (5.3%) had at least 1 SAE that was related to study drug. In the overall population, 1 participant (5.3%) had at least 1 AE that led to discontinuation of maralixibat (onset occurred at the maralixibat 280 µg/kg/day dose) and none had AEs leading to death. All participants (100%) at the highest maralixibat dose level (560 µg/kg/day) had a TEAE; however, the exposure to that dose level was much longer than any other dose (mean [SD], 555.4 [246.30] days). Generally, most participants had TEAEs at the following maralixibat dose levels: 560 µg/kg/day (100%), 280 µg/kg/day (94.7%), or 140 µg/kg/day (76.9%), and more participants had SAEs at the 280 µg/kg/day maralixibat dose compared with the other dose levels, aligning with the duration of treatment at each dose level.

The most common (occurring in >50% of participants overall) TEAEs were abdominal pain (57.9%), diarrhea (57.9%), upper respiratory tract infection (57.9%), and cough (52.6%). In the overall population, most participants had TEAEs that were mild (36.8%) or moderate (36.8%) in severity. No events of Grade 4 (life-threatening) or 5 (fatal) severity were reported. In the overall population, 4 participants (21.1%) had at least 1 severe (Grade 3) TEAE. The severe TEAEs were anemia, abdominal pain, abnormal feces, bone pain, hypoxia, post procedural hemorrhage, and hypotension. In the overall population, 15 participants (78.9%) had at least 1 TRAE. The most common (occurring in >10% of participants overall) TRAEs were abdominal pain (47.4%), diarrhea (42.1%), international normalized ratio increased (10.5%), and vitamin D deficiency (10.5%). No specific SAEs (based on preferred term) were reported in more than 1 subject. One participant (5.3%) had 1 study drug-related SAE of moderate ALT increased at the 280 µg/kg/day maralixibat dose level that led to permanent discontinuation of maralixibat and was ongoing (not recovered/not resolved) at the time of data cut-off. No other SAEs were

considered related to study drug. In the overall population, 2 participants (10.5%) had AEs that led to dose reduction as follows: abdominal pain, frequent bowel movements, and abdominal discomfort.

The AESIs included diarrhea, elevated transaminases, fat-soluble vitamin deficiency, and elevated bilirubin events as follows:

- Eleven (57.9%) participants had diarrhea and 1 (5.3%) had gastroenteritis (Note: this participant had both diarrhea and gastroenteritis events).
- One participant (5.3%) had 2 events of ALT increased
- Nine participants (47.4%) had at least 1 event of fat-soluble vitamin deficiency. The most common (reported in ≥2 participants overall) fat-soluble vitamin deficiency events were fatigue (15.8%), international normalized ratio increased (15.8%), vitamin D decreased (15.8%), epistaxis (15.8%), hematochezia (10.5%), and vitamin D deficiency (10.5%).
- One participant (5.3%) had 2 events of blood bilirubin increased (mild and moderate in severity)

Conclusions:

- Treatment with maralixibat resulted in clinically and statistically significant improvement in sBA and pruritus. The reduction (improvement) in mean change from maralixibat baseline in sBA was statistically significant in the overall population at Weeks 4 through 60, Weeks 132 through 156, and Weeks 192 through 252. A statistically significant improvement in pruritus was noted at all time points in the study from maralixibat baseline through Week 216 in the overall study population, as measured by weekly average morning severity ItchRO(Obs) scores.
- Overall, ALP, AST, total bilirubin, and direct bilirubin remained largely unchanged throughout the study. Over the course of the study duration, minor mean increases in ALT levels were observed with statistically significant increases at Weeks 24, 36, and 48.
- Overall, there were statistically significant improvements from maralixibat baseline in PedsQL Total Score (Parent), the Multidimensional Fatigue Scale Score (Parent), and the Family Impact Total Scale Score.
- Participants in this study experienced a growth benefit, as demonstrated by statistically significant improvements in height z-scores. Statistically significant improvements in weight z-scores were not observed.
- Maralixibat was safe and well tolerated. There were no life-threatening events or deaths in Study LUM001-303. Most subjects had TEAEs that were generally mild or moderate in severity.
- Overall, Grade 3 TEAEs were reported in 4 participants and included anemia, abdominal pain, abnormal feces, bone pain, and post procedural hemorrhage, hypoxia, and

hypotension. Only the events of abdominal pain and abnormal feces were considered possibly related to study drug by the investigator.

- Six participants had SAEs, of which one was considered by the investigator to be related to study drug (moderate ALT increased at the 280 µg/kg/day dose that led to permanent discontinuation of maralixibat and was ongoing at the time of data cut-off). This AE was the only event in Study LUM001-303 that led to permanent discontinuation of study drug.
- The most common TRAEs were abdominal pain, diarrhea, international normalized ratio increased, and vitamin D deficiency.
- Events of diarrhea (diarrhea and gastroenteritis) were the most common AESI, followed by fat-soluble vitamin deficiencies.

Date and Version of This Report: 20 July 2020; Interim CSR Final Version 1.0