SYNOPSIS

Name of Sponsor/Company:	Mirum Pharmaceuticals, Inc.
Name of Study Intervention:	Maralixibat chloride (formerly LUM001)
Study Title:	**INDIGO STUDY:** Open Label Study Of The Efficacy And Long Term Safety Of LUM001, An Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), In The Treatment Of Cholestatic Liver Disease In Pediatric Patients With Progressive Familial Intrahepatic Cholestasis
Study Number:	LUM001-501
Study Phase:	2
PIP and/or PSP Number (if applicable):	EMEA-001475-PIP03-17
Number of Study Center(s) and Countries:	This study was conducted at 11 sites in 4 countries (United States, United Kingdom, France, and Poland).
Publications (if any):	None.
Study Period:	This clinical study report (CSR) reports the Week 72 analyses. This report utilizes a data cut-off of 20 February 2018, representing a period of approximately 4 years from date first participant was screened of 12 February 2014; however, the focus of the report is through Week 72. A final analysis of the data will be performed after all enrolled participants have completed their final (or early termination [ET]) study visit and an addendum to this final CSR will be produced.
Methodology:	This was an open-label study in children with progressive familial intrahepatic cholestasis (PFIC) designed to evaluate the safety and efficacy of maralixibat chloride (MRX). The study was divided into 5 parts: a 4-week dose escalation period, a 4-week stable dosing period at 140 µg/kg/day, a 5-week stable dosing period at 280 µg/kg/day, a 59-week long-term exposure period, and an optional follow-up treatment period for eligible participants who chose to stay on treatment with MRX. During the optional follow-up treatment period, participants may have had their dose of MRX increased to a maximum of 560 µg/kg/day (280 µg/kg twice daily [BID]), based on ongoing efficacy (serum bile acid [sBA] level and Itch Reported Outcome [ItchRO] score) and safety assessments. Participants' participation in the optional follow-up treatment period continued until the first of the following occurred: (i) participants were eligible to enter another MRX study or (ii) MRX became available commercially.
Number of Participants (Planned and Analyzed):	It was planned to enroll a total of approximately 24 participants, including a minimum of 8 participants with PFIC1 (ATP8B1-related disease).

Screened	37	Enrolled	33	Screen Failure[a]	4
Analyzed (Safety)	33	Analyzed (mITT)	31		

Abbreviation: mITT = Modified Intent-to-treat

[a] 4 participants were screen failures under the original protocol. One additional participant was a screen failure under Protocol Amendment 3 for entry into the optional follow-up period.

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: • With a diagnosis of PFIC based on: a. Intrahepatic cholestasis manifest by total sBA >3× upper limit of normal (ULN) for age. and, b or c: b. Two documented mutant alleles in *ATP8B1*, or *ABCB11*. c. Evidence of chronic liver disease, excluding those listed in Section 16.3 of the protocol, with one or more of the following criteria: 1. Duration of biochemical or clinical abnormalities of >6 months, or 2. Pathologic evidence of progressive liver disease, or 3. Sibling of known individual affected by PFIC (predicted to be chronic). • Gamma-glutamyl transpeptidase (GGTP) <100 IU/L at Screening • Absence of the following: chronic diarrhea requiring specific intravenous fluid or nutritional intervention, surgical disruption of the enterohepatic circulation at the time at Screening, liver transplant, decompensated cirrhosis, alanine aminotransferase (ALT) >15×ULN at Screening, liver mass on imaging, history or presence of liver disease, the 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 or any other condition or abnormality which, in the opinion of the Investigator or Medical monitor, may have compromised the safety of the participant, or interfered with the participant participating in or completing the study.
Study Interventions, Dose, Mode of Administration, and Batch Number(s):	Once daily (QD) dosing of oral maralixibat solution occurred over a 13-week treatment period (comprised of an initial dose escalation period, a stable dosing period at 140 µg/kg/day, and a stable dosing period at 280 µg/kg/day) followed by a long-term exposure period. Under Protocol Amendment 4, participants continued treatment either on QD dosing, if they met pre-defined responder criteria, or were dose escalated up to a maximum daily dose of 280 µg/kg BID, i.e., 560 µg/kg/day if they didn't meet the responder criteria. Participants were dosed orally using the dosing dispenser provided, with 1.0-mL solution for children who weighed 10 kg or more at Screening, or 0.5 mL for participants who weighed less than 10 kg. Batch numbers: CA17-1098, CA15-0484, CA15-0046, AA-205525-batch-03-2013.
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 76 weeks. Participants who completed 72 weeks of treatment and were eligible to receive further treatment during the optional follow-up treatment period could continue study treatment beyond Week 72 until the first of the following occurred: (i) the participant was eligible to enter another MRX study or (ii) MRX was available commercially.

Objectives, Endpoints, Statistical Methods and Results

The objectives and endpoints that are not exploratory and are described in this report are listed in the following table. Exploratory endpoints and the exploratory objective are described in the CSR.

Study Period Objectives	Endpoints	Statistical Analyses	Results
Up to and including Week 72			
To evaluate the long-term safety and tolerability of MRX in pediatric subjects with PFIC	• TEAEs and SAEs • Clinical laboratory results • Body weight and height (as an absolute number and as a z-score for age and gender) • Study drug exposure, including average daily dose, total drug exposure, and treatment duration Population: Safety Note: vital signs, physical exam findings, concomitant medication usage, and serum AFP were safety endpoints but were not analyzed for this Week 72 analysis.	Treatment-emergent AEs, SAEs, clinical laboratory data, and body weight and height z-scores were summarized descriptively. Listings of laboratory parameter and fat-soluble vitamin levels with significant shifts from baseline were provided. Clinically-meaningful shifts in bilirubin, ALT, and fat-soluble vitamins were summarized and presented in listings. Summaries of hepatocellular carcinoma markers and fat-soluble vitamin level abnormalities were provided. Study drug exposure was summarized descriptively.	The most common treatment-related TEAEs were in the GI SOC (18 participants [54.5%]) and were mostly mild to moderate in severity and transient. Serious AEs were experienced by 14 participants (42.4%) during the 72-week observation period, and 5 participants (15.2%) had treatment-related SAEs. Thirteen participants experienced CTCAE Grade 3 or Grade 4 TEAEs during the 72-week observation period and 5 participants (15.2%) experienced TEAEs that led to permanent treatment discontinuation. No deaths were reported in the study.
To evaluate the effect of MRX on serum bile acids in pediatric subjects with PFIC at 13 weeks of treatment	Primary efficacy endpoint: • Fasting serum bile acid level change from Baseline to Week 13/ET Population: mITT	Fasting serum bile acid levels were summarized descriptively.	In the endpoint of change from baseline to Week 13/ET in sBA, numerical improvement was observed in participants with PFIC2 but not in participants with PFIC1. In the overall study population, the mean (SD) change from baseline was -23.304 µmol/L (160.9748).

To evaluate the effect of MRX on biochemical markers of cholestasis and liver disease at 13 weeks of treatment	Secondary efficacy endpoints: Change from baseline to Week 13/ET in: • ALT • total bilirubin • direct bilirubin Population: mITT	Changes from baseline to Week 13/ET in ALT, total bilirubin, and direct bilirubin were summarized descriptively.	At 13 weeks of treatment, numerical improvements from baseline were observed in ALT, total bilirubin, and direct bilirubin, in participants with PFIC2 and PFIC1.
To evaluate the effect of MRX on pruritus in pediatric subjects with PFIC at 13 weeks of treatment	Secondary efficacy endpoints: Change from baseline to Week 13/ET in: • Pruritus as measured by ItchRO(Obs) (weekly average scores, 4-week average morning scores, and 4-week average evening scores) • Pruritus as measured by ItchRO(Pt) (weekly average scores, 4-week average morning scores, and 4-week average evening scores) Population: mITT	Change from baseline to Week 13/ET in ItchRO(Obs) and ItchRO(Pt) scores were summarized descriptively.	At 13 weeks of treatment, numerical improvements from baseline were observed in the ItchRO(Obs) 4-week average morning score and ItchRO(Pt) 4-week average morning score, in participants with PFIC2 and PFIC1.

Abbreviations: AE = adverse event; AFP = alpha-fetoprotein; ALT = alanine aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; ET = early termination; GI = gastrointestinal; ItchRO(Obs) = Itch Reported Outcome (Observer); ItchRO(Pt) = Itch Reported Outcome (Patient); MRX = maralixibat chloride; mITT = Modified Intent-to-treat; PFIC = progressive familial intrahepatic cholestasis; SAE = serious adverse events; SD = standard deviation; SOC = system organ class; TEAE = treatment-emergent adverse event.

Summary of Results and Conclusions:

Demography and Baseline Characteristics:

Overall, there were slightly more females than males in the study (19 females [57.6%] and 14 males [42.4%]). The mean (SD) overall age was 4.2 years (3.24), and participants ranged from 1 to 13 years of age. There were 26 participants (78.8%) who were White, 3 participants (9.1%) who were Asian, 3 participants (9.1%) whose race was not reported, and 1 participant (3.0%) who reported more than one race.

In the overall population, the median time since the original diagnosis of PFIC was 32.2 months with a range of 4.6-127.0 months, 23 participants (69.7%) had no known family history of PFIC, and 28 participants (84.8%) had used therapies to treat itch in the past, most frequently oral therapies (27 participants [81.8%]). The most commonly reported itch treatments used previously were oral enzyme inducers and oral ursodeoxycholic acid (UDCA), reported by 22 participants (66.7%) each. A summary of CSS scores showed the majority of participants had evident abrasions (21 participants [63.6%]) or evident cutaneous mutilation, hemorrhage, or scarring (5 participants [15.2%]).

Exposure:

During the 72-week observation period, the mean (SD) daily dose for the overall study population was 244 (33.4) µg/kg/day, total drug exposure was 112,041 (34,131.6) µg/kg, and treatment duration was 452 (113.8) days.

Efficacy Results:

In the primary endpoint of change from baseline to Week 13/ET in sBA, numerical improvement was observed in participants with PFIC2 (mean [SD] change from baseline, -38 [177.7] µmol/L) but not in participants with PFIC1. In the overall study population, the mean (SD) change from baseline was -23 (161.0) µmol/L.

In the secondary endpoints of change from baseline to endpoint (Week 13/ET), numerical improvements were observed in the overall study population in mean (SD) ItchRO(Obs) 4-week average morning score (-0.7 [0.65]), ItchRO(Pt) 4-week average morning score (-0.6 [0.57]), ALT (-9 [61.8] U/L), total bilirubin (-0.2 [1.65] mg/dL), and direct bilirubin (-0.1 [1.12] mg/dL). Numerical improvements in each of the parameters listed above were noted in participants with PFIC2 and PFIC1.

In the endpoints of change from baseline to endpoint (Week 72/ET), numerical improvements were observed in the overall study population in mean (SD) sBA (-2 [146.0] µmol/L) and ALT (-12 [59.6] µmol/L). Numerical improvements were noted in sBA (mean [SD], -10 [162.8] µmol/L) and ALT (mean [SD], -19 [65.0] U/L) in participants with PFIC2, but not participants with PFIC1.

In the endpoints of change from baseline to endpoint (Week 48/ET), numerical improvements were observed in the overall study population in ItchRO(Obs) 4-week average morning score (mean [SD], -0.9 [0.94]) and ItchRO(Pt) 4-week average morning score (mean [SD], -1.0 [0.69]). Numerical improvements were noted in ItchRO(Obs) 4-week average morning score (mean [SD], -1.0 [0.96]) and ItchRO(Pt) 4-week average morning score (mean [SD], -1.0 [0.80]) in participants

with PFIC2. Numerical improvements in ItchRO(Obs) and ItchRO(Pt) were also observed in participants with PFIC1.

In posthoc analyses evaluating the primary and secondary efficacy endpoints, 6 of 19 PFIC2 participants with bile salt export protein (BSEP) mutations associated with residual function (non-truncating PFIC2 [nt-PFIC2]) showed a pattern of response across multiple endpoints. An analysis of multiparameter response of those participants having a) a 70% reduction or normalization of sBA and b) reduction of 1.0 point in ItchRO(Obs) was conducted. Six participants with nt-PFIC2 met the multiparameter response criteria across multiple timepoints from Week 4 to Week 72 and exhibited reductions in ALT, AST, and bilirubin in cases where those values were elevated at baseline. Height and weight z-score changes from baseline in participants who responded to MRX treatment on multiple parameters differed in a clinically significant fashion from participants who did not at all time points beyond Week 26, with treatment responders demonstrating positive mean z-scores changes from baseline (i.e., catch-up growth) vs. non- or partial responders who experienced negative mean z-score changes from baseline (i.e., further growth retardation).

Safety Results:

A summary of treatment-emergent adverse events (TEAEs) during the 72-week observation period is presented below.

Category	Weeks 0-72 (Days 1-504) (N=33) n (%)
PFIC Type: Overall	
Participants with at Least 1:	
TEAE	33 (100.0)
TEAE Potentially Related to Study Drug[a]	23 (69.7)
Serious TEAE	14 (42.4)
Serious TEAE Potentially Related to Study Drug[a]	5 (15.2)
TEAE Leading to Study Drug Discontinuation	5 (15.2)
TEAE Leading to Death	0

Abbreviations: AE = adverse event; n = number in a given category; N = number of participants; PFIC = progressive familial intrahepatic cholestasis; TEAE = treatment-emergent adverse event

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

Note: Percentages are 100*n/N. Treatment-emergent adverse events (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 considers both the date of the last dose prior to drug interruption and the actual last dose.

No deaths were reported during the conduct of the study. All participants experienced at least 1 TEAE. The most frequently reported TEAEs were in the infections and infestations SOC, followed by the GI disorders SOC. Preferred terms reported most often included the following:

pyrexia (17 participants [51.5%]), diarrhea (16 participants [48.5%]), cough (13 participants [39.4%]), and vomiting (13 participants [39.4%]).

Overall, reported TEAEs were generally mild or moderate in severity. Thirteen participants experienced a severe (Common Terminology Criteria for Adverse Events [CTCAE] Grade 3) or life-threatening (CTCAE Grade 4) TEAE during the 72-week observation period. Two participants experienced CTCAE Grade 4 TEAEs during the 72-week observation period: hyperbilirubinemia (considered potentially related to study drug by the investigator) was experienced by 1 participant; and ALT increased and AST increased (considered unlikely related to study drug) were experienced by 1 participant. A total of 11 participants (33.3%) experienced TEAEs of maximum severity Grade 3 during the 72-week observation period. The severe (Grade 3) TEAEs included the following: blood bilirubin increased (3 participants [9.1%]); diarrhea, disease progression, and pruritus (2 participants [6.1%]) each; abdominal pain, diarrhea hemorrhagic, pancreatic insufficiency, pancreatitis, irritability, hyperbilirubinemia, upper limb fracture, bilirubin conjugated increased, iron deficiency, malnutrition, convulsion, and encephalopathy (1 participant [3.0%] each).

Treatment-emergent AEs potentially related to study drug were experienced by 23 participants (69.7%) overall, with a lower incidence in participants with PFIC1 (3 participants [37.5%]) compared with participants with PFIC2 (20 participants [80.0%]). Gastrointestinal events (from the GI disorders SOC) were the most frequently reported treatment-related TEAEs (18 participants [54.5%]). The most frequently reported preferred terms in the GI disorders SOC included the following: diarrhea (10 participants [30.3%]); abdominal pain (7 participants [21.2%]); and abdominal pain upper (6 participants [18.2%]), vomiting (5 participants [15.2%]), frequent bowel movements (4 participants [12.1%]), and feces pale (2 participants [6.1%]).

Serious AEs (SAEs) were experienced by 14 participants (42.4%) overall, including 4 participants (50.0%) with PFIC1 and 10 participants (40.0%) with PFIC2. Gastrointestinal events (from the GI disorders SOC) were the most frequently reported SAEs (6 participants [18.2%]). The only SAEs reported for more than 1 participant were abdominal pain and diarrhea, each experienced by 2 participants (6.1%). Serious AEs potentially related to study drug were experienced by 5 participants (15.2%) overall, with a similar incidence in participants with PFIC1 (1 participant [12.5%]) and PFIC2 (4 participants [16.0%]). The treatment-related SAEs were reported for 1 participant each and included abdominal pain, abdominal pain upper, diarrhea, pancreatitis, blood bilirubin increased, and INR increased. Each of the treatment-related SAEs required hospitalization with the exception of blood bilirubin increased.

A total of 5 participants (15.2%) experienced TEAEs that led to permanent treatment discontinuation, including disease progression (2 participants [6.1%]), blood bilirubin increased (2 participants [6.1%]), and pancreatitis (1 participant [3.0%)]. Of the TEAEs that led to permanent treatment discontinuation, only the TEAE of pancreatitis was considered potentially related to study drug. All of the TEAEs that led to permanent treatment discontinuation were experienced by participants with PFIC2.

A total of 27 participants (81.8%) experienced TEAEs of special interest in the GI disorders SOC, 31 participants (93.9%) experienced TEAEs of special interest that were conditions associated with liver deterioration, and 18 participants (54.5%) experienced TEAEs of special interest that were fat-soluble vitamin deficiency events.

Conclusions:

- Numerical reductions in sBA were observed at 13 weeks and 72 weeks of treatment with MRX in the overall group and the subgroup of participants with PFIC2. In the primary endpoint of change from baseline to Week 13/ET in sBA, numerical improvement was observed in participants with PFIC2 but not in participants with PFIC1. Similar results were observed for the endpoint of change from baseline to Week 72/ET.
- At 13 weeks of treatment, numerical improvements from baseline were observed in the ItchRO(Obs) 4-week average morning score, ItchRO(Pt) 4-week average morning score, ALT, total and direct bilirubin, in participants with PFIC2 and PFIC1.
- Participants with PFIC2 continued to show numerical improvement in sBA and ALT at 72 weeks of treatment, and in ItchRO(Obs) 4-week average morning score and ItchRO(Pt) 4-week average morning score at 48 weeks of treatment. Participants with PFIC1 continued to show numerical improvement in the ItchRO(Obs) 4-week average morning score and ItchRO(Pt) 4-week average morning score at 48 weeks of treatment.
- Posthoc analyses revealed that 6 participants with nt-PFIC2 mutations showed sustained multiparameter response with normalization or >70% reduction from baseline in sBA, full control of pruritus or reduction from baseline of ≥1.0 on the ItchRO scale as well as a normalization of transaminases and bilirubin (if elevated at baseline). These treatment responders demonstrated a catch-up growth, as manifested by a positive height and weight z-score changes from baseline over the 72-week observation period, as compared to a further growth deficit (negative mean height/weight z-score changes from baseline) in non- or partial responders.
- Serious AEs were experienced by 14 participants (42.4%) during the 72-week observation period. The only SAEs reported for more than 1 participant were abdominal pain and diarrhea, each experienced by 2 participants (6.1%). Treatment-related SAEs were experienced by 5 participants (15.2%). The treatment-related SAEs were reported for 1 participant each and included abdominal pain, abdominal pain upper, diarrhea, pancreatitis, blood bilirubin increased, and INR increased.
- Overall, reported TEAEs were generally mild or moderate in severity. Thirteen participants experienced a severe (CTCAE Grade 3) or life-threatening (CTCAE Grade 4) TEAE during the 72-week observation period. Two participants experienced CTCAE Grade 4 TEAEs during the 72-week observation period: hyperbilirubinemia (considered potentially related to study drug) was experienced by 1 participant; and ALT increased and AST increased (considered unlikely related to study drug) were experienced by 1 participant. A total of 11 participants (33.3%) experienced TEAEs of maximum severity Grade 3 during the 72-week observation period.
- Treatment-emergent AEs potentially related to study drug were experienced by 23 participants (69.7%) overall. Gastrointestinal events were the most frequently reported treatment-related TEAEs (18 participants [54.5%]).
- A total of 5 participants (15.2%) experienced TEAEs that led to permanent treatment discontinuation.

- No deaths were reported in the study.
- Maralixibat was safe and well tolerated.

Date and Version of This Report: CSR Final v1.0, 07-May-2020