TITLE PAGE

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
Short Title:	**INDIGO**: Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi) in the Treatment of Cholestatic Liver Disease in Pediatric Patients with Progressive Familial Intrahepatic Cholestasis
Study Intervention:	Maralixibat chloride (formerly LUM001)
Indication:	Treatment of patients with progressive familial intrahepatic cholestasis (PFIC)
Study Sponsor:	Mirum Pharmaceuticals, Inc. 950 Tower Lane, Suite 1050 Foster City, California 94404
Study Number:	LUM001-501
Study Phase:	2
Study Initiation Date:	12 February 2014 (first participant first visit)
Data Report Date:	20 February 2018 (date of data cut-off)
Regulatory Agency Identifier Number:	EuDRA CT No: 2013-003833-14
Report Date:	**Document Version** / **Date** CSR Final v1.0 / 07-May-2020

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

TABLE OF CONTENTS

APPENDICES

List of In-Text Tables

List of In-Text Figures

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	DEFINITION/EXPLANATION
7αC4	7α hydroxyl-4-cholesten-3-one; an indirect method of bile acid synthesis
ADE	afternoon dose escalation
AE	adverse event
AFP	alpha-fetoprotein
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ASBT	apical sodium-dependent bile acid transporter
ASBTi	apical sodium-dependent bile acid transporter inhibitor
AST	aspartate aminotransferase
BID	twice daily
BMI	body mass index
BSEP	bile salt export protein
CFB	change from baseline
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CRA	clinical research associate
CRF	case report form
CRL	Clinical Reference Laboratory
CRO	contract research organization
CSR	clinical study report
CSS	Clinician Scratch Score
CTCAE	Common Terminology Criteria for Adverse Events
EASL	European Association for the Study of the Liver
ET	early termination
eTMF	electronic trial master file
EU	European Union
fBA	fecal bile acid
FDA	Food and Drug Administration
FGF	Fibroblast growth factor
GCP	Good Clinical Practice
GGTP	gamma-glutamyl transpeptidase
GI	gastrointestinal
HDL-C	high-density lipoprotein cholesterol
HIPAA	Health Insurance Portability and Accountability Act

ABBREVIATION	DEFINITION/EXPLANATION
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INR	International normalized ratio
IRB/IEC	institutional review board/independent ethics committee
ItchRO™	Itch Reported Outcome
ItchRO(Obs)™	Itch Reported Outcome (Observer)
ItchRO(Pt)™	Itch Reported Outcome (Patient)
LDL-C	low-density lipoprotein cholesterol
LLOQ	lower limit of quantitation
m	number of participants with data at each visit
MARS	molecular adsorbent recirculating system
Max	maximum
mITT	Modified Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum
MRX	maralixibat chloride
n	number in a given category
N	number of participants
NA	not applicable
NEC	not elsewhere classified
nt	non-truncating
PFIC	progressive familial intrahepatic cholestasis
PD	pharmacodynamics
PEBD	partial external biliary diversion
PK	pharmacokinetics
PM	project manager
PP	Per-protocol
PT	prothrombin time
QA	quality assurance
QD	once daily
QoL	quality of life
RBP	retinol-binding protein
SAE	serious adverse event
SAP	statistical analysis plan
sBA	serum bile acid
SD	standard deviation
SOC	system organ class (MedDRA)

ABBREVIATION	DEFINITION/EXPLANATION
TEAE	treatment-emergent adverse event
UDCA	ursodeoxycholic acid
UK	United Kingdom
ULN	upper limit of normal
ULOQ	upper limit of quantitation

ETHICS

Independent Ethics Committee and/or Institutional Review Board

- The protocol, protocol amendments, ICF, investigator brochure, and other relevant documents (e.g., advertisements) were submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study was initiated.

- Any amendments to the protocol required IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Ethical Conduct of the Study

This study was conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines

- Applicable ICH GCP Guidelines

- Applicable laws and regulations

Patient Information and Consent/Assent

- The investigator or his/her representative explained the nature of the study to the participant or his/her legally authorized representative and answered all questions regarding the study.

- Participants were informed that their participation was voluntary. Participants or their legally authorized representative were required to sign a statement of informed consent or assent that met the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center. Since this was a pediatric study, in addition to the written informed consent, the assent of the child was also obtained.

- The medical record included a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent also signed the ICF.

- Participants were re-consented to the most current version of the ICF(s) during their participation in the study.

- A copy of the ICF(s) was provided to the participant or the participant's legally authorized representative.

1. INTRODUCTION

PFIC is an autosomal recessive liver disorder characterized by intrahepatic cholestasis due to defects in bile transportation from hepatocytes to bile canaliculi. Its exact prevalence is unknown but the disease is estimated to affect one in every 50,000 to 100,000 births (Davit-Spraul et al., 2009). PFIC represents 10% to 15% of causes of cholestasis in children (Gunaydin et al., 2018) and 10% to 15% of indications for liver transplantations in children (Davit-Spraul et al., 2009).

PFIC is categorized into several subtypes, including the main subtypes PFIC1, PFIC2, and PFIC3, caused by mutations in the genes *ATP8B1*, *ABCB11*, and *ABCB4*, respectively (Amer et al., 2014). All PFIC subtypes share the main clinical manifestations of cholestasis and pruritus and all subtypes of PFIC are associated with early mortality, morbidity, and devastating impact on patients' QoL. Due to a lack of treatment options, the majority of patients ultimately require liver transplantation. PFIC1 and PFIC2 are aggressive diseases; in patients with PFIC2, native liver survival is only 46% at 10 years and of 33% at 18 years, overall (van Wessel et al., 2018).

PFIC1, caused by mutations in *ATP8B1*, and also referred to as Byler disease, comprises approximately 10% to 20% of the PFIC population (Alissa et al., 2008; Davit-Spraul et al., 2009).

PFIC2, caused by mutations in *ABCB11*, is the most common subtype and is diagnosed in approximately 50% to 60% of all PFIC patients (Al Mehaidib et al., 2013). *ABCB11* encodes a liver-specific transporter called BSEP that is responsible for exporting bile acids into the bile canaliculi against extreme concentration gradients. Mutations in the *ABCB11* gene cause various degrees of deficiency in BSEP and hence various degrees of bile acid excretion capabilities. PFIC2, also referred to as BSEP deficiency, is categorized into non-truncating (mild to moderate phenotype with residual BSEP function) or truncating mutations (severe phenotype without residual BSEP function or complete absence of BSEP).

Currently, there are no approved pharmacologic therapies to treat the signs and symptoms of PFIC or the underlying liver disease. According to the European Association for the Study of the Liver (EASL) "no medical therapy of proven benefit for the long-term prognosis of PFIC exists" (EASL, 2009). Current pharmacotherapeutic options include off-label use of UDCA, cholestyramine, rifampicin, and other anti-pruritic medications (Gunaydin et al., 2018; Düll and Kremer 2019). The hydrophilic bile acid UDCA is used as an initial treatment for many PFIC subtypes to promote biliary flow. However, response rates are limited to approximately 50% for patients with PFIC3 and even fewer patients with PFIC1 and PFIC2. Other anti-pruritic medications often bring only partial or temporary symptom relief, bear significant safety challenges in this patient population (e.g., hepatotoxicity with rifampicin) or have poor palatability (e.g., cholestyramine). In the absence of a curative treatment option, surgical approaches such as PEBD or liver transplant are commonly employed to address symptoms and improve QoL as well as the underlying liver disease but come with a heavy burden for the patients/families and society as well as with significant medical and surgical complications.

Maralixibat chloride (maralixibat) is a minimally absorbed, potent, highly selective inhibitor (IC50 = 0.3 nM) of the apical sodium dependent bile acid transporter/ileal bile acid transporter/solute carrier family 10 (sodium/bile acid co-transporter family) member 2 (ASBT/IBAT/SLC10A2). This transmembrane protein transporter, localized on the luminal surface of ileal enterocytes, is present in the terminal 25% of the small intestine and mediates

uptake of conjugated bile acids across the brush border membrane of the enterocyte. Bile acids from the enterocyte are transported to the liver via the portal vein and then secreted back into the bile in a system known as the enterohepatic circulation. Approximately 95% of bile acids that enter the gut lumen are recycled via the liver to the gallbladder where they are stored for future release into the duodenum. Maralixibat-mediated blockade of intestinal reabsorption of bile acids by ASBT interrupts the enterohepatic circulation, thereby increasing fecal bile acid excretion and lowering sBA levels.

ASBT inhibition has the potential to reduce cholestasis due to PFIC and of its associated signs and symptoms, like cholestatic pruritus and growth deficit. Recent natural history data have demonstrated that the reduction of sBA levels through surgical interruption of the enterohepatic circulation (e.g., PEBD) was strongly associated with improved native liver survival long-term, particularly in patients with non-truncating PFIC2 (van Wessel et al., 2020). Pharmacological interruption of the enterohepatic circulation using the ASBT inhibitor maralixibat therefore has disease-modifying potential to increase native liver survival in the non-truncating PFIC2 patient population while minimizing systemic off-target effects due to its minimally absorbed nature.

2. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
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 • Analyses that were planned for the final analysis but not performed for the Week 72 analysis: o Vital signs o Physical exam findings o Concomitant medication usage o Serum AFP
• To evaluate the effect of MRX on serum bile acids in pediatric subjects with PFIC at 13 weeks of treatment	<u>Primary efficacy endpoint:</u> • Fasting sBA level change from Baseline to Week 13/ET
• To evaluate the effect of MRX on biochemical markers of cholestasis and liver disease at 13 weeks of treatment	The secondary efficacy endpoints included the change from baseline to Week 13/ET in: • ALT • Total bilirubin • Direct bilirubin • Planned for the final analysis but not analyzed for the Week 72 analysis: o ALP o AST
• To evaluate the effect of MRX on pruritus in pediatric subjects with PFIC at 13 weeks of treatment	The secondary efficacy endpoints included the 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

Abbreviations: AE = adverse event; AFP = alpha-fetoprotein; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ET = early termination; ItchRO(Obs) = Itch Reported Outcome (Observer); ItchRO(Pt) = Itch Reported Outcome (Patient); MRX = maralixibat chloride; PFIC = progressive familial intrahepatic cholestasis; SAE = serious adverse events; TEAE = treatment-emergent adverse event.

3. INVESTIGATIONAL PLAN

3.1. Overview of Study Design

This was an open-label, single-arm study in children with PFIC (GGTP <100 IU/L) designed to evaluate the safety and efficacy of 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 been eligible for BID dosing based on efficacy as measured by sBA level and ItchRO score, and may have had their dose of MRX increased to a maximum of 560 µg/kg/day (280 µg/kg BID). Participants' participation in the optional follow-up treatment period could continue until the first of the following occurred: (i) participants were eligible to enter another MRX study or (ii) MRX was available commercially.

An interim analysis of key safety and efficacy parameters was performed after the first 12 participants who met the PP Population definition completed the Week 13 study visit. A second interim analysis was performed after all evaluable participants completed the Week 48 (or ET) study visit. A Week 72 analysis, the subject of this report, was performed using a data cut-off date of 20 February 2018, under Protocol Amendment 4 (or the Early Termination visit). Subsequent interim analyses were to be performed in yearly intervals. The study design is depicted in Figure 3-1, Figure 3-2, Figure 3-3, Figure 3-4, and Figure 3-5. Additional details are available in the study protocol (Appendix 9.1).

Figure 3-1: Study Design (up to and including Week 72)

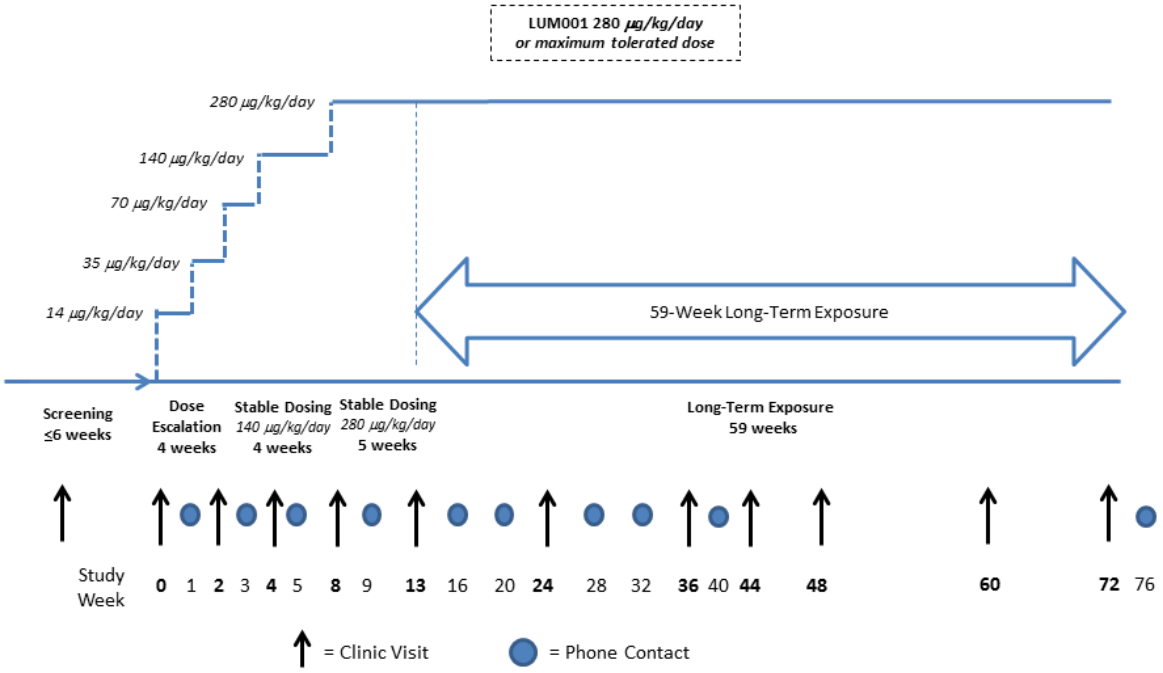


Figure 3-2: Optional Follow-up Treatment Period (post-Week 72; <7 days from last MRX dose between Protocol Amendment 2 and Protocol Amendment 3)

Applies to the following participant population:

Participants who experienced no interruption in MRX dosing, or interruption <7 days between Protocol Amendment 2 and Protocol Amendment 3.

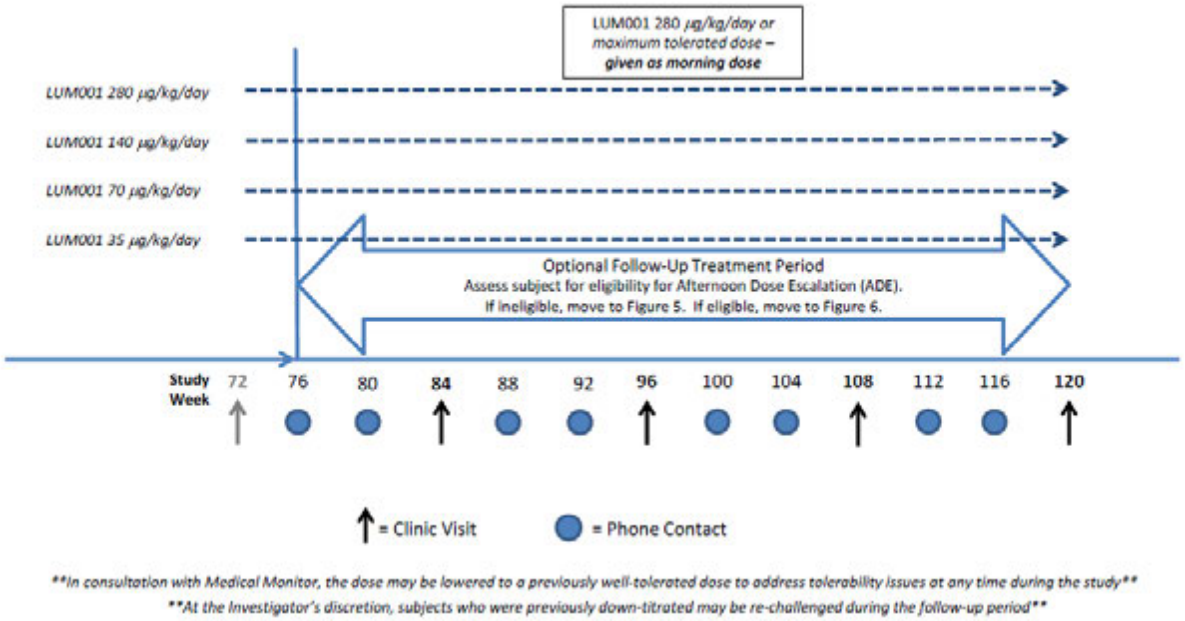


Figure 3-3: Optional Follow-up Treatment Period (post-Week 72; ≥7 days from last MRX dose between Protocol Amendment 2 and Protocol Amendment 3)

Applies to the following participant population:

Participants who experienced an interruption in MRX dosing ≥7 days between Protocol Amendment 2 and Protocol Amendment 3.

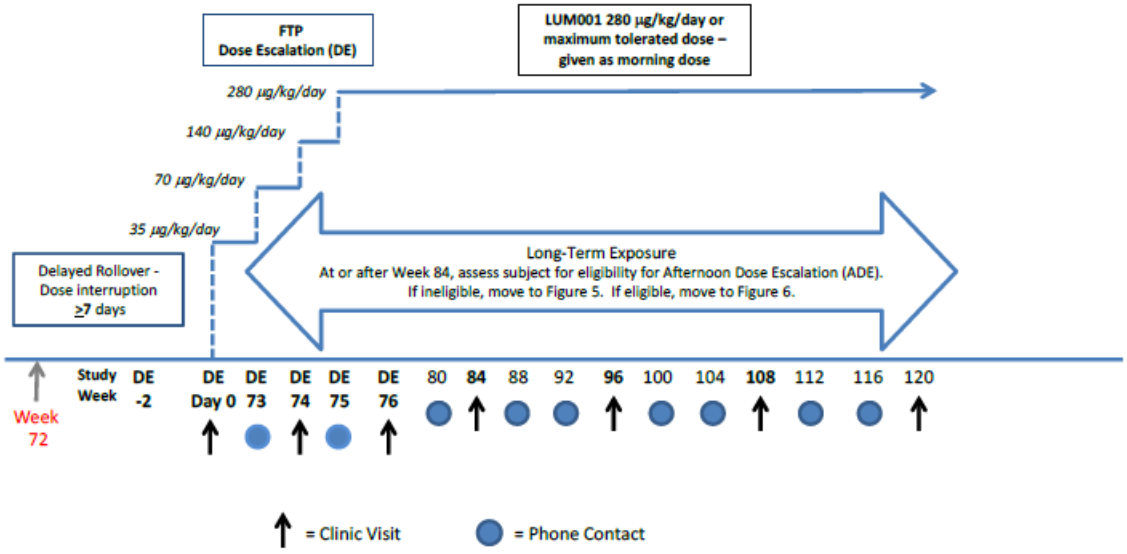


Figure 3-4: Optional Follow-up Treatment Period (post-Week 72; ≥7 days from last MRX dose between Protocol Amendment 3 and Protocol Amendment 4)

Applies to the following participant population:

Participants who experienced an interruption in MRX dosing ≥7 days between Protocol Amendment 3 and Protocol Amendment 4.

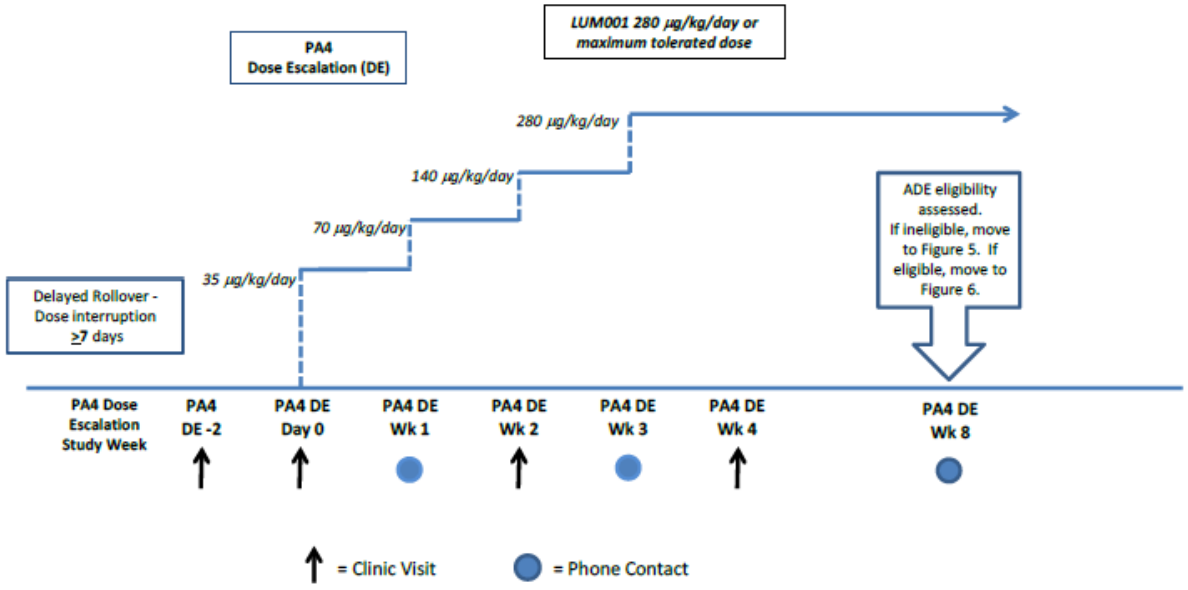
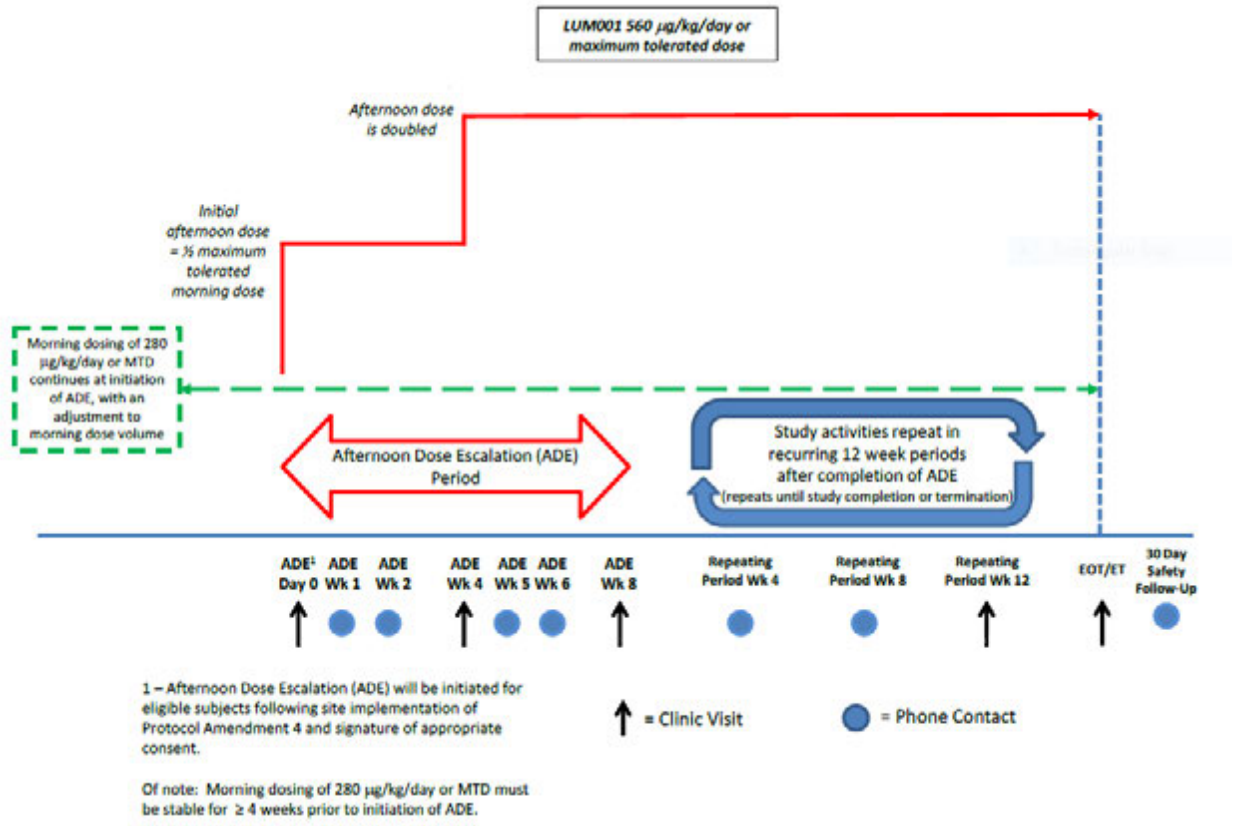


Figure 3-5: Optional Follow-up Treatment under Protocol Amendment 4, with Afternoon Dose Escalation

Applies to the following participant population:

Participants whose sBA levels have not normalized and/or whose ItchRO score is ≥1.5 and therefore qualify for introduction of afternoon dosing.



3.1.1. Discussion of Study Design

The therapeutic rationale and rationale for selection of study drug dose and the schedule of administration are provided in Sections 4.1 and 4.5, respectively, of the study protocol (Appendix 9.1).

3.1.2. Changes in Study Conduct

Amendment 1:

(UK and EU) Substantial changes made to the protocol were to: limit propylene glycol exposure to within the recommended limits; modify testing requirements for monitoring the liver chemistry test; and add evaluations in the event of a confirmed elevation in ALT or total bilirubin level.

(US) In addition to the changes noted for the UK and EU amendment, substantial changes were made to clarify the frequency for the evaluation of MRX plasma levels.

Amendment 2:

Substantial changes made to the protocol were to: modify inclusion and exclusion criteria regarding serum bile acid levels, surgical procedures, and prohibited medications; increase the number of evaluable participants; increase the number of clinic visits and duration of treatment from 48 weeks to 72 weeks reached the 48-week visit.

Amendment 3:

Substantial changes made to the protocol were to: add an Optional Follow-up Treatment Period (After Week 72) that allowed eligible participants treated in the LUM001-501 study to continue on treatment after Week 72 until the first of the following occurred: (i) up to 52 weeks of additional treatment (Week 124), or (ii) in the event that a new study opened to enrollment; and added an objective to obtain safety and efficacy data in participants treated long term on MRX including genotyping characteristics.

Amendment 4:

Substantial changes made to the protocol were to allow continued participation in the Optional Follow-Up Treatment Period, beyond what was previously described in Protocol Amendment 3; clarify that study treatment in the Optional Follow-up Treatment Period could continue until the first of the following occurred: (i) the participants were eligible to enter another MRX study or (ii) MRX was available commercially; clarify that eligible participants who had previously discontinued from the study could re-enter and receive study treatment in the Optional Follow-up Treatment Period (after Week 72); and describe objectives and assessments of the Optional Follow-up Treatment Period, including the following: exploration of a BID dosing regimen and higher daily dosing of MRX; identification of genetic indicators of treatment response, including use of exome sequencing; assessment of AFP levels, a marker of hepatocellular carcinoma; assessment of the palatability of the MRX formulation in all patients, by-proxy in patients <4 years old and by patient questionnaire in children ≥4 years old; and an exploratory objective to allow the possibility of analysis of serum markers of treatment response using metabolomic and proteomic analysis on previously collected serum samples.

A higher maximum dosing level (maximum daily dose of 280 µg/kg BID, i.e., 560 µg/kg/day; (maximum of 25 mg BID) was selected for the Optional Follow-up Treatment Period because of the findings in healthy volunteers (Study SHP625-101) of higher fecal bile acid (fBA) excretion on higher maralixibat doses and BID dosing regimen up to 100 mg QD and 50 mg BID with a comparable safety profile across the tested dose range.

During the BID dosing regimen, the dose was to be taken at least 30 minutes prior to the main morning and evening meal in order to cover the luminal bile acid release associated with meals.

Participants with sBA levels above the ULN and/or ItchRO score ≥1.5 were eligible to start BID dosing.

If a participant experienced intolerance (e.g., GI symptoms such as diarrhea, abdominal pain, cramping) at any time during the study, the physician Investigator in consultation with the Medical Monitor may have lowered the dose for the remainder of the study.

Amendment 4.1:

Substantial changes made to the protocol were to reflect the change of sponsorship from Lumena Pharmaceuticals LLC to Mirum Pharmaceuticals, Inc; document the change in Medical Monitor; and reduce the interval that new medications used to treat pruritus were prohibited to between Baseline until Week 13 (time point for primary analysis).

All changes in the conduct of the study were implemented by protocol amendments, as described in the study protocol (Appendix 9.1).

3.2. Investigators and Study Administrative Structure

A list of principal investigators and their affiliations and information regarding other important study personnel and organizations that were critical to the conduct of the study are provided in Appendix 9.4.

3.3. Selection of Study Population

3.3.1. Inclusion/Exclusion Criteria

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 serum bile acid >3× 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).
- 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, ALT >15×ULN at Screening, liver mass on imaging, history or presence of liver disease, 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.

Participants who completed the protocol through the Week 72 visit with no major safety concerns, did not have surgical disruption of the enterohepatic circulation, had not used an investigational drug (other than MRX) or biologic or medical device within 30 days prior to re-entry or 5 half-lives

of the study agent, whichever was longer, and if female, had a negative urine or serum pregnancy test at the time of entry into the follow-up period, were eligible to participate in the optional follow-up treatment period study.

Detailed inclusion and exclusion criteria are provided Sections 7.1, 7.2, and 7.3 of the study protocol (Appendix 9.1).

3.3.2. Removal of Participants from Intervention or Study

The specific criteria and procedures for adjustment of study drug dose and early discontinuation from study intervention or withdrawal from the study are described in Sections 10.6 and 10.7 of the study protocol (Appendix 9.1).

3.4. Study Intervention

3.4.1. Study Interventions Administered

All participants received MRX, up to 280 µg/kg/day until Protocol Amendment 4, when 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.

During the QD dosing period, each participant received either 1.0 mL (participants weighing ≥10 kg) or 0.5 mL (participants weighing <10 kg) of solution containing MRX orally, administered as a daily morning dose. If a participant experienced intolerance (e.g., GI symptoms such as diarrhea, abdominal pain, cramping) at any time during the study, the physician investigator in consultation with the Medical Monitor may have lowered the dose for the remainder of the study.

Dosing Periods:

- 4-week dose escalation [Dose Level 1-4]
- 4-week stable dosing at 140 µg/kg/day
- 5-week stable dosing at 280 µg/kg/day (participants who tolerated Dose Level 4)
- 59-week long-term exposure

Dose Escalation Period:

During the first 4 weeks of the study, the dose escalation period, the dose was increased at weekly intervals starting with Dose Level 1, up to Dose Level 4, to acclimate the participant to the study drug.

Stable Dosing Period:

Following the 4-week dose escalation period, participants continued MRX dosing through Week 8 using Dose Level 4, or the highest tolerated dose below Dose Level 4. For those participants who tolerated Dose Level 4, at Week 8, the dose was increased to Dose Level 5 until Week 13.

Long-term Exposure Period:

Participants continued to receive MRX during the long-term exposure dosing treatment

period according to the highest dose achieved during the stable dosing treatment period. Dose adjustments were made as needed due to intolerance or changes in the participant's body weight. Participants who were previously down-titrated may have been re-challenged during the long-term exposure period.

Optional Follow-up Treatment Period (Post-Week 72):

Under Protocol Amendment 4, participants eligible for the optional follow-up treatment period either continued receiving the same dose level of MRX or started BID dosing. Eligibility for BID dosing was determined based on efficacy as measured by sBA level and ItchRO score.

Participants could continue to receive study drug until they were eligible to enter another MRX study or until MRX is available commercially, whichever occurred first.

Maralixibat was prepared by a central pharmacy based on the participant's weight at screening. The appropriate volume of diluent was added by the central pharmacy pharmacist prior to shipping maralixibat to the site. The sponsor provided the Investigator with packaged study drug labeled in accordance with specific country regulatory requirements. Standard dosing dispensers were provided for oral administration of study drug.

Additional details regarding study treatment are provided in Sections 10.1 and 5.5.2 of the study protocol (Appendix 9.1). The justification for the doses selected is described in Section 4.5 of the study protocol (Appendix 9.1).

The manufacturing lot numbers for the study intervention available to be dispensed in this study as well as the diluent vial lot numbers are provided in Appendix 9.6.

3.4.2. Measures to Minimize Bias

Not applicable.

3.4.3. Study Intervention Compliance

The method used to assess study intervention compliance is described in Section 10.2 of the study protocol (Appendix 9.1).

3.4.4. Prior, Concomitant, or Post-intervention Therapy

The medications allowed or disallowed before and during study intervention, including any exceptions to these requirements, are described in Sections 10.3, 7.2, and 7.3 of the study protocol (Appendix 9.1).

3.5. Study Assessments and Procedures

3.5.1. Planned Measurements and Timing of Assessments

The specific efficacy and safety variables assessed, and their schedule and measurement/collection methods are provided in the Schedule of Procedures and described in Efficacy Variables (Section 12.2.9.1), Safety Analyses (Section 12.2.4), and Study Procedures (Section 8) in the study

protocol (Appendix 9.1). The collection and assessment of safety information during the study (evaluation, definitions, recording, and reporting of AEs, SAEs, and other reportable safety events) is detailed in Serious and Non-serious Adverse Event Reporting (Section 11) in the study protocol (Appendix 9.1).

3.5.2. Appropriateness of Measures

The endpoints used in this study (e.g., efficacy, safety, and other endpoints) were standard, generally reliable, and relevant to the objectives set forth in the study protocol (Appendix 9.1).

3.5.3. Additional Summary of Specific Assessments

Not applicable.

3.6. Data Quality Assurance

3.6.1. Study Monitoring

Study centers were monitored by the sponsor or CRO. Centers were visited and the Investigator and/or study staff were contacted by telephone frequently. Monitors were responsible for reviewing adherence to the protocol; compliance with GCP; and the completeness, accuracy, and consistency of the data. Direct access to participant medical and laboratory records was permitted to verify entries on the study-specific CRFs.

3.6.2. Investigator Meetings and Staff Training

Investigator staff training was provided by the sponsor or CRO during investigator meetings, initiation and routine monitoring visits. The sponsor/CRO organized investigator and clinical research associate meetings before study start and during the study to provide information on the investigational product, the study rationale and design, responsibilities under ICH/FDA/GCP, and training on the detailed study requirements.

3.6.3. Standardization of Laboratory Procedures

Clinical Reference Laboratory (CRL) served as the central laboratory, laboratory supply and sample management vendor; responsible for the analysis of safety and clinical labs and the management and receipt, storage (as applicable), and shipment of samples from sites to the specialty labs. CRL utilized an online lab results reporting system (OASIS) that was accessible by site staff, monitors, project managers and the sponsor.

Where local laboratories were used, their participation in internal and external quality control, quality assurance, and accreditation schemes was evaluated by the study monitors. Documentation of inter-laboratory standardization methods and laboratory QA procedures is provided in Appendix 9.10.

3.6.4. Investigator Responsibilities

The investigators were responsible for all data entered in the CRFs and documented their review and approval of the data by signing a form verifying the validity and completeness of the data. The investigator was responsible for appropriate retention of essential study documents.

3.6.5. Clinical Data Management

Case report form data were captured via data entry by study center personnel in Datalabs®. Data quality checks were applied using manual and/or electronic verification methods. An audit trail to support data query resolution and any modification to the data was maintained.

3.6.6. Clinical Quality Assurance Audits

Audits of this study were included as part of the independent sponsor or CRO quality assessment performed by the sponsor or CRO/independent contractor. Audit certificates for this study are provided in Appendix 9.8.

3.7. Statistical Analysis

3.7.1. Statistical Analysis Plan

This CSR reports the Week 72 analyses. This was the third planned analysis. The planned analyses, comparisons, statistical tests, and determination of sample size are described in the final version of the SAP (Appendix 9.9). The tables, figures, and listings presented in Appendix 8.1 and Appendix 8.2 of this CSR include data collected throughout the study at the time of data cut-off (20 February 2018), including study visits subsequent to Week 72. A final analysis of the data will be performed after all enrolled participants have completed their final (or ET) study visit and an addendum to this final CSR will be produced.

3.7.2. Changes in the Planned Analyses Prior to Unblinding or Database Lock

All changes in the planned analyses for the study were implemented by the SAP or protocol amendments, as described in the SAP (Appendix 9.9) and study protocol (Appendix 9.1), with the exception of the following:

Tables that were planned for the third interim analysis but were not produced:

Table 14.2.4.2	MMRM Analysis of Serum Bile Acid Level (µmol/L) by Study Visit (Modified Intent-to-Treat Population)
Table 14.2.9.3	MMRM Analysis of ItchRO (Observer) Pruritus Average Scores by Study Visit (Modified Intent-to-Treat Population)

Tables produced that were not planned for the third interim analysis but were defined in the SAP:

Table 14.1.1.1	Subject Disposition (All Subjects)
Table 14.2.4.1.2	Change from Baseline Serum Bile Acid Level (µmol/L) by Study Visit BID Dosing Only (Modified Intent-to-Treat Population)

Posthoc Tables and Figures produced:

Table 14.4.1	Posthoc Analysis: Non-truncating PFIC2 (BSEP deficient) Multiparameter Responders
Figure 14.4.1	Posthoc Analysis: Change from Baseline in Height z-score Over Time in Responders vs. Partial/Non-responders

Figure 14.4.2 Posthoc Analysis: Change from Baseline in Weight z-score Over Time in Responders vs. Partial/Non-responders

Listings produced that were not planned for the third interim analysis but were defined in the SAP:

Listing 16.1.3 Subject Profile: Pediatric Quality of Life Inventory – Total Scale and Summary Scores (Safety Population)

Listing 16.1.4 Subject Profile: Efficacy Labs (Serum Bile Acid, Lipids, Fat-Soluble Vitamins, and Coagulation) (Safety Population)

Listing 16.2.1.1 Analysis Populations and Treatment (All Subjects)

Listing 16.2.1.2.2 Subject Disposition (All Subjects Assigned Treatment)

Listing 16.2.2.2 Major Protocol Deviations (All Subjects Enrolled)

Listing 16.2.4.1 Demographics and Informed Consent (All Subjects Enrolled)

Listing 16.2.4.2 Medical History (All Subjects Assigned Treatment)

Listing 16.2.4.3 PFIC Disease History (All Subjects Assigned Treatment)

Listing 16.2.4.4 Prior and Concomitant Medications (Safety Population)

Listing 16.2.5.1 Study Drug Accountability and Compliance (All Subjects Enrolled)

Listing 16.2.5.2 Study Drug Exposure (Safety Population)

Listing 16.2.6.1 Total Serum Bile Acid (Safety Population)

Listing 16.2.6.2 Clinician Scratch Score (Safety Population)

Listing 16.2.6.3.1 Itch Reported Outcomes (Subject and Caregiver) (Safety Population)

Listing 16.2.6.3.2 Itch Reported Outcomes (Subject and Caregiver) Weekly Average Scores (Safety Population)

Listing 16.2.6.4 PIC, CIC, and CGTB (Safety Population)

Listing 16.2.6.5 Efficacy Laboratory Tests (Safety Population)

Listing 16.2.7.1 Adverse Events (Safety Population)

Listing 16.2.7.2.1 Adverse Events of Special Interest: Gastrointestinal Events (Safety Population)

Listing 16.2.7.2.4 Adverse Events of Special Interest: Fat-Soluble Vitamin Deficiency Events (Safety Population)

Listing 16.2.7.3 Serious Adverse Events (Safety Population)

Listing 16.2.7.4 Adverse Events Leading to Study Drug Discontinuation (Safety Population)

Listing 16.2.7.5 Life-Threatening Adverse Events (Safety Population)

Listing 16.2.7.6 Adverse Events Causing Death (Safety Population)

Listing 16.2.7.7 Vital Signs (Safety Population)

Listing 16.2.7.8 Physical Examination (Safety Population)

Listing 16.2.8.1 Clinical Laboratory Tests: Clinical Chemistry (Safety Population)

Listing 16.2.8.7 Clinical Laboratory Tests: Coagulation (Safety Population)

3.7.3. Changes Following Study Unblinding/Database Lock and Posthoc Analyses

Posthoc analyses are listed in Section 3.7.2

4. STUDY PARTICIPANTS

In this CSR, the terms participant and subject are used interchangeably.

4.1. Disposition of Participants

A summary of participant disposition through Week 72 is presented in Table 4-1.

A total of 37 PFIC patients were screened for the study. Four of these patients were screen failures under the original protocol. A total of 33 participants were enrolled in the study and subsequently had genotyping performed. Of the 33 participants, 8 were PFIC1 and 25 were PFIC2. Two pairs of siblings (all with PFIC2) from 2 families were enrolled in the study. Three participants (9.1%) were dose reduced during the study.

A total of 22 participants (66.7%) completed study treatment through Week 72. Eleven participants (33.3%) discontinued early prior to Week 72: 3 participants (9.1%) due to an AE; 2 participants (6.1%) each due to progressive disease and withdrawal by caregiver; and 1 participant (3.0%) each due to non-compliance with study drug, physician decision, withdrawal by subject, and other reason. A single patient was a screen failure for entry under Protocol Amendment 3.

Table 4-1: Participant Disposition and Reason for Discontinuation (All Participants)

Status or Variable	PFIC Type		Overall
	PFIC1	PFIC2	
Screened for Eligibility	8	25	37
Screen Failure under Original Protocol[a]			4
Screen Failure under Protocol Amendment			1
Enrolled	8	25	33
Number of families with siblings enrolled in the study	0	2	2
Total number of siblings[b]	0	4	4
Safety Population[c]	8	25	33
mITT Population[d] n (%)	8 (100.0)	23 (92.0)	31 (93.9)
Down-Titrated During Study n (%)	1 (12.5)	2 (8.0)	3 (9.1)
Completed Study Treatment through Week 72 n (%)	6 (75.0)	16 (64.0)	22 (66.7)
Discontinued Early Prior to Week 72 n (%)	2 (25.0)	9 (36.0)	11 (33.3)
Reason for Discontinuation Prior to Week 72 n (%)			
Adverse event	0	3 (12.0)	3 (9.1)
Death	0	0	0
Lost to follow-up	0	0	0
Non-compliance with study drug	0	1 (4.0)	1 (3.0)
Physician decision	1 (12.5)	0	1 (3.0)
Pregnancy	0	0	0
Progressive disease	0	2 (8.0)	2 (6.1)

Status or Variable	PFIC Type		Overall
	PFIC1	PFIC2	
Protocol violation	0	0	0
Study terminated by sponsor	0	0	0
Withdrawal by caregiver	1 (12.5)	1 (4.0)	2 (6.1)
Withdrawal by subject	0	1 (4.0)	1 (3.0)
Other[e]	0	1 (4.0)	1 (3.0)

Source: Appendix 8.1, Table 14.1.1.1

Abbreviations: mITT = modified intent-to-treat; n = number in a given category; PFIC = progressive familial intrahepatic cholestasis; PP = per-protocol

a Participants who did not meet eligibility criteria, or otherwise chose not to participate in the study (or optional treatment extension period), before or after assignment but before the first dose of study drug in the study (or under the optional treatment extension period).

b Each sibling was considered for the Safety Population. One sibling within a family was considered for the mITT population for use in efficacy analyses.

c The Safety Population included all participants assigned to study treatment who received any amount of study drug.

d The mITT Population included all participants in the Safety Population who had at least 1 post-baseline primary efficacy assessment.

e Other: the participant underwent liver transplantation with a main indication poor quality of life due to severe intractable pruritus, not responding to any available medical treatment including MRX (Appendix 8.2, Listing 16.2.1.2.2.

Note: Percentages are based on the number of participants in the Safety Population.

4.2. Protocol Deviations

Protocol deviations to be recorded during the study included the following:

- ICF process or signature/version issue
- Violation of inclusion/exclusion criteria
- Study/protocol procedures
- Dosing error
- Excluded medication
- Visit window deviation
- Other deviation from study procedures

Other protocol deviations may have been identified during the study.

Protocol deviations were not analyzed for this Week 72 analysis.

4.3. Populations Analyzed

Table 4-1 shows the number of participants in the Safety Population and the mITT Population. A total of 33 participants (8 with PFIC1 and 25 with PFIC2) were included in the Safety Population,

which included all participants who were assigned to study treatment and received any amount of study drug. A total of 31 (93.9%) participants were included in the mITT Population, which included all participants in the Safety Population who had at least 1 post-baseline primary efficacy assessment. Two participants, both with PFIC2, were excluded from the mITT Population.

4.4. Demographic and Other Baseline Characteristics

4.4.1. Demography

Table 4-2 summarizes the demographics of the Safety Population at baseline. Overall, there were slightly more females than males (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.

Table 4-2: Demographics and Baseline Characteristics (Safety Population)

Variable Statistic or Category	PFIC Type PFIC1 (N=8)	PFIC Type PFIC2 (N=25)	Overall (N=33)
Age (years)[a]			
n	8	25	33
Mean (SD)	3.0 (2.00)	4.6 (3.49)	4.2 (3.24)
Median	2.0	4.0	3.0
Min, Max	1, 7	1, 13	1, 13
Age Category[a] n (%)			
<2 years	1 (12.5)	6 (24.0)	7 (21.2)
2 to 4 years	5 (62.5)	10 (40.0)	15 (45.5)
5 to 8 years	2 (25.0)	4 (16.0)	6 (18.2)
9 to 12 years	0	4 (16.0)	4 (12.1)
13 to 18 years	0	1 (4.0)	1 (3.0)
Gender n (%)			
Male	6 (75.0)	8 (32.0)	14 (42.4)
Female	2 (25.0)	17 (68.0)	19 (57.6)

Variable Statistic or Category	PFIC Type PFIC1 (N=8)	 PFIC2 (N=25)	 Overall (N=33)
Height z-score			
n	8	25	33
Mean (SD)	-3.0 (1.47)	-1.3 (0.98)	-1.7 (1.32)
Median	-2.5	-1.5	-1.7
Min, Max	-6.1, -1.6	-2.8, 0.8	-6.1, 0.8
Weight z-score			
n	8	25	33
Mean (SD)	-2.7 (2.82)	-0.6 (0.88)	-1.1 (1.77)
Median	-1.8	-0.3	-0.8
Min, Max	-9.1, -0.3	-2.7, 0.6	-9.1, 0.6
Race n (%)			
American Indian or Alaska Native	0	0	0
Asian	2 (25.0)	1 (4.0)	3 (9.1)
Black or African American	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
White	6 (75.0)	20 (80.0)	26 (78.8)
More than 1 race	0	1 (4.0)	1 (3.0)
Not reported	0	3 (12.0)	3 (9.1)

Source: Appendix 8.1, Tables 14.1.2.1.1, 14.3.4.7, and 14.3.4.9
Abbreviations: Max = maximum; Min = minimum; n = number in a given category; N = number of participants; PFIC = progressive familial intrahepatic cholestasis; SD = standard deviation
a Age at time of baseline visit.

4.4.2. Baseline Disease Characteristics

A summary of baseline disease characteristics is presented in Table 4-3. 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 (Appendix 8.1, Table 14.1.3.1.1). Overall, 23 participants (69.7%) had no known family history of PFIC. A total of 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 (i.e., reported by >10% of participants) included the following: oral enzyme inducers and oral ursodeoxycholic acid (UDCA), reported by 22 participants (66.7%) each; oral antihistamines, 15 participants (45.5%); oral bile acid binding resins, 12 participants (36.4%); oral opiate antagonists, 8 participants (24.2%); oral serotonin antagonists, 7 participants (21.2%); and oral anticonvulsants, 6 participants (18.2%).

Table 4-3: Disease History and Baseline Disease Characteristics – Diagnosis (Safety Population)

Variable Statistic or Category	PFIC Type PFIC1 (N=8)	PFIC Type PFIC2 (N=25)	Overall (N=33)
Time Since Original Diagnosis of PFIC (months)			
n	8	25	33
Mean (SD)	33.7 (23.48)	44.0 (34.81)	41.5 (32.40)
Family History of PFIC n (%)			
Yes	3 (37.5)	3 (12.0)	6 (18.2)
No	5 (62.5)	18 (72.0)	23 (69.7)
Unknown	0	4 (16.0)	4 (12.1)
Used Anything to Treat Itch in the Past n (%)			
Yes	7 (87.5)	21 (84.0)	28 (84.8)
No	1 (12.5)	4 (16.0)	5 (15.2)
Type of Therapy Used to Treat Itch in the Past n (%)			
Topical	1 (12.5)	4 (16.0)	5 (15.2)
Oral	7 (87.5)	20 (80.0)	27 (81.8)
Other	2 (25.0)	9 (36.0)	11 (33.3)

Variable Statistic or Category	PFIC Type PFIC1 (N=8)	 PFIC2 (N=25)	 Overall (N=33)
Specific Therapy Used to Treat Itch in the Past n (%)			
Topical Antihistamines	1 (12.5)	2 (8.0)	3 (9.1)
Topical Calcineurin Inhibitors	0	1 (4.0)	1 (3.0)
Topical Capsaicin	0	0	0
Topical Corticosteroids	0	3 (12.0)	3 (9.1)
Topical Local Anesthetics	1 (12.5)	1 (4.0)	2 (6.1)
Topical Menthol	0	1 (4.0)	1 (3.0)
Topical Salicylic Acid	0	0	0
Oral Androgens	0	0	0
Oral Anticholestatic Agents	0	0	0
Oral Anticonvulsants	1 (12.5)	5 (20.0)	6 (18.2)
Oral Antidepressants	0	2 (8.0)	2 (6.1)
Oral Antihistamines	3 (37.5)	12 (48.0)	15 (45.5)
Oral Anti-oxidants	0	1 (4.0)	1 (3.0)
Oral Binding Resins	2 (25.0)	10 (40.0)	12 (36.4)
Oral Cannabinoid Agonist	0	0	0
Oral Colchicine	0	0	0
Oral Enzyme Inducers	5 (62.5)	17 (68.0)	22 (66.7)
Oral Immunosuppressants	0	0	0
Oral Opiate Antagonists	2 (25.0)	6 (24.0)	8 (24.2)
Oral Serotonin Antagonists	2 (25.0)	5 (20.0)	7 (21.2)
Oral Ursodeoxycholic Acid (UDCA)	5 (62.5)	17 (68.0)	22 (66.7)
Other Hemofiltration (MARS)	0	1 (4.0)	1 (3.0)
Other Nasal Biliary Drainage	0	1 (4.0)	1 (3.0)
Other Phototherapy	0	0	0
Other Plasmapheresis	0	0	0

Source: Appendix 8.1, Table 14.1.3.1.1
Abbreviations: MARS = molecular adsorbent recirculating system; n = number in a given category; N = number of participants; PFIC = progressive familial intrahepatic cholestasis; SD = standard deviation; UDCA = ursodeoxycholic acid.

A summary of CSS scores and ItchRO (both observer and patient) weekly average score, 4-week average morning score, and 4-week average evening score is provided in Table 4-4. The summary of CSS scores showed the majority of participants had evident abrasions (score 3; 21 participants [63.6%]) or evident cutaneous mutilation, hemorrhage, or scarring (score 4; 5 participants [15.2%]). The baseline ItchRO(Obs) mean (SD) scores were 2.3 (0.83), 2.3 (0.88), and 2.2 (0.89) for the weekly average score, 4-week average morning score, and 4-week average evening score, respectively. The baseline ItchRO(Pt) mean (SD) scores were 2.2 (0.91), 2.1 (0.95), and 2.1 (0.93)

for the weekly average score, 4-week average morning score, and 4-week average evening score, respectively.

Table 4-4: Disease History and Baseline Disease Characteristics – Itch Assessments (Safety Population)

Variable Statistic or Category	PFIC Type PFIC1 (N=8)	PFIC Type PFIC2 (N=25)	Overall (N=33)
Clinician Scratch Scale Score[a]			
n	8	25	33
Mean (SD)	2.8 (0.46)	2.9 (0.93)	2.8 (0.83)
Median	3.0	3.0	3.0
Min, Max	2, 3	0, 4	0, 4
0, n (%)	0	1 (4.0)	1 (3.0)
1, n (%)	0	1 (4.0)	1 (3.0)
2, n (%)	2 (25.0)	3 (12.0)	5 (15.2)
3, n (%)	6 (75.0)	15 (60.0)	21 (63.6)
4, n (%)	0	5 (20.0)	5 (15.2)
ItchRO(Obs) Weekly Average Score[b]			
n	8	25	33
Mean (SD)	2.1 (0.75)	2.3 (0.86)	2.3 (0.83)
Median	2.1	2.3	2.2
Min, Max	1.1, 3.4	0.1, 3.8	0.1, 3.8
ItchRO(Pt) Weekly Average Score[b]			
n	2	9	11
Mean (SD)	1.4 (0.35)	2.4 (0.91)	2.2 (0.91)
Median	1.4	2.4	2.2
Min, Max	1.1, 1.6	0.4, 3.6	0.4, 3.6
ItchRO(Obs) 4-Week Average Morning Score[c]			
n	8	25	33
Mean (SD)	2.4 (0.96)	2.3 (0.87)	2.3 (0.88)
Median	2.0	2.4	2.3
Min, Max	1.1, 3.6	0.4, 3.8	0.4, 3.8

Variable Statistic or Category	PFIC Type PFIC1 (N=8)	PFIC Type PFIC2 (N=25)	Overall (N=33)
ItchRO(Pt) 4-Week Average Morning Score[c]			
n	2	9	11
Mean (SD)	1.6 (0.38)	2.2 (1.0)	2.1 (0.95)
Median	1.6	2.2	2.1
Min, Max	1.3, 1.8	0.3, 3.8	0.3, 3.8
ItchRO(Obs) 4-Week Average Evening Score[c]			
n	8	25	33
Mean (SD)	2.0 (0.80)	2.3 (0.92)	2.2 (0.89)
Median	2.1	2.1	2.1
Min, Max	1.1, 3.5	0.3, 3.8	0.3, 3.8
ItchRO(Pt) 4-Week Average Evening Score[c]			
n	2	9	11
Mean (SD)	1.2 (0.03)	2.3 (0.92)	2.1 (0.93)
Median	1.2	2.0	1.9
Min, Max	1.2, 1.2	0.6, 3.7	0.6, 3.7

Source: Appendix 8.1, Table 14.1.3.1.1

Abbreviations: ItchRO(Obs) = Itch Reported Outcome (Observer); ItchRO(Pt) = Itch Reported Outcome (Patient); Max = maximum; Min = minimum; n = number in a given category; N = number of participants; PFIC = progressive familial intrahepatic cholestasis; SD = standard deviation

a The clinician scratch scale uses a 5-point scale, where 0 = none, 1 = rubbing or mild scratching when undistracted, 2 = active scratching without evident skin abrasions, 3 = abrasion evident, 4 = cutaneous mutilation, hemorrhage, and scarring evident.

b ItchRO Weekly Average Score = sum of daily scores divided by the number of days ItchRO was completed, using the 7 days prior to the baseline visit. Caregivers for all participants completed the observer instrument: ItchRO(Obs). Children at least 9 years of age completed the patient instrument: ItchRO(Pt). Children between the ages of 5 and 8 years of age completed the ItchRO(Pt) with the assistance of their caregiver. There is no ItchRO(Pt) report for participants under the age of 5.

c ItchRO 4-Week Average Morning/Average Evening Score = sum of morning/evening scores divided by the number of days ItchRO was completed, based upon up to 28 days prior to the baseline visit.

Note: Percentages are 100*n/N.

Table 4-5 summarizes laboratory assessments at baseline.

Table 4-5: Disease History and Baseline Disease Characteristics – Laboratory Assessments (Safety Population)

Variable Statistic or Category	PFIC Type PFIC1 (N=8)	PFIC Type PFIC2 (N=25)	Overall (N=33)
Serum Bile Acid (µmol/L)			
n	8	25	33
Mean (SD)	262 (99.6)	381 (150.0)	352 (147.4)
Median	216	408	374
Min, Max	160, 423	34, 602	34, 602
Alkaline Phosphatase (U/L)			
n	8	25	33
Mean (SD)	697 (220.0)	467 (150.3)	522 (193.8)
Median	674	455	483
Min, Max	310, 974	227, 765	227, 974
Aspartate Aminotransferase (U/L)			
n	8	25	33
Mean (SD)	77 (23.8)	162 (164.0)	141 (147.2)
Median	66	97	94
Min, Max	51, 114	28, 672	28, 672
Alanine Aminotransferase (U/L)			
n	8	25	33
Mean (SD)	56 (29.7)	125 (118.0)	108 (107.4)
Median	37	91	85
Min, Max	32, 109	13, 438	13, 438
Gamma Glutamyl Transferase (U/L)			
n	8	25	33
Mean (SD)	18 (6.1)	29 (23.8)	26 (21.3)
Median	16	17	17
Min, Max	11, 27	6, 89	6, 89

Variable Statistic or Category	PFIC Type PFIC1 (N=8)	PFIC Type PFIC2 (N=25)	Overall (N=33)
Bilirubin (mg/dL)			
n	8	25	33
Mean (SD)	5.5 (5.13)	2.1 (1.75)	2.9 (3.20)
Median	3.0	1.6	1.8
Min, Max	0.9, 15.1	0.1, 6.5	0.1, 15.1
Direct Bilirubin (mg/dL)			
n	8	25	33
Mean (SD)	4.0 (3.67)	1.6 (1.36)	2.2 (2.33)
Median	2.2	1.3	1.3
Min, Max	0.7, 10.0	0.1, 4.6	0.1, 10.0
Cholesterol (mg/dL)			
n	8	25	33
Mean (SD)	113 (23.2)	203 (53.1)	181 (61.4)
Median	112	196	189
Min, Max	79, 155	105, 282	79, 282
Triglycerides (mg/dL)			
n	8	25	33
Mean (SD)	125 (31.3)	181 (77.4)	168 (72.9)
Median	133	181	158
Min, Max	64, 162	44, 409	44, 409
7 alpha-hydroxy-4-cholesten-3-one (C4) (ng/mL)			
n	8	25	33
Mean (SD)	2.7 (2.19)	4.6 (9.14)	4.2 (8.03)
Median	2.5	2.7	2.7
Min, Max	0.2, 5.8	0.2, 47.3	0.2, 47.3
Retinol (ug/dL)			
n	8	25	33
Mean (SD)	73.5 (35.98)	48.6 (22.18)	54.6 (27.74)
Median	73.5	43.0	46.0
Min, Max	17.2, 119.0	14.3, 89.0	14.3, 119.0

Variable Statistic or Category	PFIC Type PFIC1 (N=8)	PFIC Type PFIC2 (N=25)	Overall (N=33)
25-Hydroxyvitamin D (ng/mL)			
n	8	23	31
Mean (SD)	37.9 (17.33)	27.5 (11.02)	30.2 (13.44)
Median	39.5	29.0	29.0
Min, Max	10.0, 66.9	9.2, 52.0	9.2, 66.9
Alpha Tocopherol (mg/dL)			
n	8	25	33
Mean (SD)	0.34 (0.167)	0.49 (0.351)	0.45 (0.320)
Median	0.35	0.46	0.43
Min, Max	0.12, 0.65	0.04, 1.31	0.04, 1.31
International Normalized Ratio			
n	8	25	33
Mean (SD)	1.08 (0.089)	1.18 (0.344)	1.16 (0.304)
Median	1.05	1.10	1.10
Min, Max	1.0, 1.2	0.9, 2.7	0.9, 2.7

Source: Appendix 8.1, Table 14.1.3.1.1

Abbreviations: LLOQ = lower limit of quantitation; Max = maximum; Min = minimum; n = number in a given category; N = number of participants; PFIC = progressive familial intrahepatic cholestasis; SD = standard deviation; ULOQ = upper limit of quantitation

Note: Percentages are 100*n/N. For analysis of laboratory tests, one-half of the LLOQ was used for values reported as <LLOQ or ≤LLOQ; the ULOQ was used for values reported as >ULOQ or ≥ULOQ.

4.4.3. Medical History and Concurrent Illnesses

Not applicable.

4.5. Prior, Concomitant, and Post-intervention Therapy

Not applicable.

4.6. Exposure and Study Intervention Compliance

4.6.1. Exposure

Table 4-6 summarizes investigational product exposure during the 72-week observation period.

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

treatment duration were generally similar in participants with PFIC1 compared with participants with PFIC2.

Table 4-6: Summary of Exposure to Investigational Product (Safety Population)

Variable Statistic	Weeks 0-72 (N=33)
PFIC Type: Overall	
Average Daily Dose (µg/kg/day)	
n	33
Mean (SD)	244 (33.4)
Median	259
Min, Max	107, 268
Total Drug Exposure (µg/kg)	
n	33
Mean (SD)	112,041 (34,131.6)
Median	129,619
Min, Max	20,713, 139,013
Treatment Duration (days)	
n	33
Mean (SD)	452 (113.8)
Median	504
Min, Max	112, 533
PFIC Type: PFIC1	
Average Daily Dose (µg/kg/day)	
n	8
Mean (SD)	236 (53.2)
Median	260
Min, Max	107, 261
Total Drug Exposure (µg/kg)	
n	8
Mean (SD)	105,049 (39,211.8)
Median	131,856
Min, Max	49,693, 135,093

Variable Statistic	Weeks 0-72 (N=33)
Treatment Duration (days)	
n	8
Mean (SD)	445 (120.4)
Median	508
Min, Max	213, 518
PFIC Type: PFIC2	
Average Daily Dose (µg/kg/day)	
n	25
Mean (SD)	247 (25.1)
Median	259
Min, Max	170, 268
Total Drug Exposure (µg/kg)	
n	25
Mean (SD)	114,278 (32,913.8)
Median	128,786
Min, Max	20,713, 139,013
Treatment Duration (days)	
n	25
Mean (SD)	455 (114.0)
Median	504
Min, Max	112, 533

Source: Appendix 8.1, Table 14.3.1
Abbreviations: Max = maximum; Min = minimum; n = number in a given category; N = number of participants; PFIC = progressive familial intrahepatic cholestasis; SD = standard deviation
Note: Percentages are 100*n/N. Study drug exposure estimates exclude dosing gaps due to the participant being off study (between protocol amendments).

A categorical summary of investigational product exposure during the 72-week observation period is provided in Table 4-7.

All participants had a treatment duration greater than 13 weeks (86 days), the majority of participants (84.8%) had a treatment duration greater 48 weeks (322 days), and 22 participants (66.7%) had a treatment duration of at least 72 weeks. The incidence of participants in each treatment duration category were generally similar in participants with PFIC1 compared with participants with PFIC2.

Table 4-7: Categorical Summary of Exposure to Investigational Product (Safety Population)

Variable Category	Overall (N=33) n (%)
PFIC Type: Overall	
Treatment Duration (days)	
≤13 Weeks (≤86 days)	0
>13 Weeks (>86 days)	33 (100.0)
>48 Weeks (>322 days)	28 (84.8)
>72 Weeks (>490 days)	22 (66.7)
PFIC Type: PFIC1	
Treatment Duration (days)	
≤13 Weeks (≤86 days)	0
>13 Weeks (>86 days)	8 (100.0)
>48 Weeks (>322 days)	6 (75.0)
>72 Weeks (>490 days)	6 (75.0)
PFIC Type: PFIC2	
Treatment Duration (days)	
≤13 Weeks (≤86 days)	0
>13 Weeks (>86 days)	25 (100.0)
>48 Weeks (>322 days)	22 (88.0)
>72 Weeks (>490 days)	16 (64.0)

Source: Appendix 8.1, Table 14.3.1
Abbreviations: n = number in a given category; N = number of participants; PFIC=progressive familial intrahepatic cholestasis
Note: Percentages are 100*n/N. Study drug exposure estimates excluded dosing gaps due to the participant being off study (between protocol amendments).

4.6.2. Dose Modification

Not applicable.

4.6.3. Measurement of Study Intervention Compliance

Table 4-8 summarizes treatment compliance during the 72-week observation period. Mean (SD) compliance for the overall study population was 98.9 (4.43)% during Weeks 0-13 and 98.0 (5.98)% during Weeks 14-72. Treatment compliance was generally similar in participants with PFIC1 compared with participants with PFIC2.

Table 4-8: Study Drug Compliance (Safety Population)

Study Phase Statistic	PFIC Type		
	PFIC1 (N=8)	PFIC2 (N=25)	Overall (N=33)
Weeks 0-13			
n	8	25	33
Mean (SD)	96.0 (8.75)	99.9 (0.36)	98.9 (4.43)
Median	100.0	100.0	100.0
Min, Max	74.7, 100.0	98.9, 100.0	74.7, 100.0
Weeks 14-72			
n	8	25	33
Mean (SD)	99.1 (0.94)	97.6 (6.84)	98.0 (5.98)
Median	99.3	99.8	99.8
Min, Max	97.1, 100.0	66.8, 100.0	66.8, 100.0

Source: Appendix 8.1, Table 14.1.5.1

Abbreviations: Max = maximum; Min = minimum; n = number in a given category; N = number of participants; PFIC = progressive familial intrahepatic cholestasis; SD = standard deviation

Note: Compliance (%) = 100* (Number of days a dose was taken / Expected treatment duration in days) was calculated for each study phase. Expected treatment duration (days) = Date of last visit during the specified study phase - First day of dosing during the specified study phase + 1 day - # days participant was off study between protocol amendments. Number of days a dose was taken = Expected treatment duration (days) - Number of days a dose was missed (during the specified study phase; excluding dosing gaps due to the participant being off study between protocol amendments). For early terminated participants, the date of last dose was considered, rather than the date of the last visit during the study phase in which the participant early terminated.

5. EVALUATION OF RESPONSE TO STUDY INTERVENTION

5.1. Efficacy

The results of the Week 72 analyses described in the SAP are presented in this CSR. The final analyses will be performed in the future as described in the SAP after all enrolled participants have completed their final (or ET) study visit, and an addendum to this final CSR will be produced.

5.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint was the change from baseline to endpoint (Week 13/ET) in fasting sBA level.

The baseline mean (SD) sBA concentration was 262 (99.6) µmol and 393 (144.6) µmol for participants with PFIC1 and PFIC2, respectively (Appendix 8.1, Table 14.2.4.1.1).

Table 5-1 summarizes the changes from baseline to endpoint (Week 13/ET) in sBA concentrations in the mITT Population. A numerical increase in sBA concentrations (mean [SD] change from baseline, 18 [95.7] µmol/L) was observed in participants with PFIC1. In contrast, a numerical reduction (improvement) was noted in participants with PFIC2 (mean [SD] change from baseline, -38 [177.7] µmol/L).

A subset of participants exhibited 70% or greater reductions or normalization in sBA levels across multiple time points and are further described in Section 5.1.4.

In the overall study population, the mean (SD) change from baseline was -23 (161.0) µmol/L.

A by-participant listing of select efficacy labs and itch/scratch scores is presented in Appendix 8.2, Listing 16.1.1.

Table 5-1: Primary Efficacy Endpoint: Serum Bile Acid Level – Change from Baseline to Endpoint (Week 13/ET) (Modified Intent-to-Treat Population)

	PFIC Type					
	PFIC1		PFIC2		Overall	
Statistic	Observed	CFB	Observed	CFB	Observed	CFB
Serum Bile Acid (µmol/L)						
n	8	8	23	23	31	31
Mean	280	18	355	-38	336	-23
SD	100.4	95.7	220.5	177.7	197.8	161.0
Median	294	38	400	-11	343	-3
Min, Max	102, 405	-117, 149	1, 881	-463 279	1, 881	-463, 279

Source: Appendix 8.1, Table 14.2.4.1.1
Abbreviations: CFB = change from baseline, defined as post-baseline value minus baseline value; ET = early termination; Max = maximum; Min = minimum; n = number in a given category; PFIC = progressive familial intrahepatic cholestasis; SD = standard deviation
Note: The Week 13/ET time point represents the last post-baseline value obtained within 7 days of the last dose prior to the Week 13 visit.

5.1.2. Secondary Efficacy Endpoints

Table 5-2 presents a summary of the secondary efficacy endpoints change from baseline to endpoint (Week 13/ET) in ALT, total bilirubin, direct bilirubin, ItchRO(Obs), and ItchRO(Pt).

The baseline mean (SD) ALT concentration was 56 (29.7) U/L and 126 (120.0) U/L for participants with PFIC1 and PFIC2, respectively (Appendix 8.1, Table 14.2.6.1.1). A smaller numerical reduction in ALT was observed in participants with PFIC1 (-2 [29.1] U/L) compared to participants with PFIC2 (mean [SD] change from baseline, -11 [70.1] U/L). In the overall study population, the mean (SD) change from baseline was -9 (61.8) U/L.

The baseline mean (SD) total bilirubin concentration was 5.5 (5.13) mg/dL and 2.0 (1.70) mg/dL for participants with PFIC1 and PFIC2, respectively (Appendix 8.1, Table 14.2.7.1.1). Numerical reductions in total bilirubin were noted in participants with PFIC1 (-0.8 [2.95] mg/dL) and PFIC2 (mean [SD] change from baseline, -0.0 [0.90] mg/dL). In the overall study population, the mean (SD) change from baseline was -0.2 (1.65) mg/dL.

The baseline mean (SD) direct bilirubin concentration was 4.0 (3.67) mg/dL and 1.6 (1.29) mg/dL for participants with PFIC1 and PFIC2, respectively (Appendix 8.1, Table 14.2.8.1.1). A greater numerical reduction in direct bilirubin was noted in participants with PFIC1 (mean [SD] change from baseline, -0.3 [1.93] mg/dL) compared to participants with PFIC2 (-0.0 [0.72] mg/dL). In the overall study population, the mean (SD) change from baseline was -0.1 (1.12) mg/dL.

The baseline mean (SD) ItchRO(Obs) 4-week average morning score was 2.3 (0.96) and 2.3 (0.91) for participants with PFIC1 and PFIC2, respectively (Appendix 8.1, Table 14.2.9.1.1). A greater

numerical reduction in ItchRO(Obs) 4-week average morning score was observed in participants with PFIC1 (mean [SD] change from baseline, -0.8 [0.83] compared to participants with PFIC2 (-0.7 [0.59]). In the overall study population, the mean (SD) change from baseline was -0.7 (0.65).

The baseline mean (SD) ItchRO(Pt) 4-week average morning score was 1.6 (0.38) and 2.1 (1.17) for participants with PFIC1 and PFIC2, respectively (Appendix 8.1, Table 14.2.10.1.1). A smaller numerical reduction in ItchRO(Pt) 4-week average morning score was observed in participants with PFIC1 (mean [SD] change from baseline, -0.4 [0.65] compared to participants with PFIC2 -0.7 [0.57]). In the overall study population, the mean (SD) change from baseline was -0.6 (0.57).

Table 5-2: Secondary Efficacy Endpoints: Change from Baseline to Endpoint (Week 13/ET) (Modified Intent-to-Treat Population)

	PFIC Type					
	PFIC1		PFIC2		Overall	
Statistic	Observed	CFB	Observed	CFB	Observed	CFB
Alanine Aminotransferase (U/L)						
n	8	8	23	23	31	31
Mean	54	-2	115	-11	99	-9
SD	27.6	29.1	128.0	70.1	113.8	61.8
Total Bilirubin (mg/dL)						
n	8	8	23	23	31	31
Mean	4.7	-0.8	2.0	-0.0	2.7	-0.2
SD	2.89	2.95	1.85	0.90	2.42	1.65
Direct Bilirubin (mg/dL)						
n	8	8	23	23	31	31
Mean	3.8	-0.3	1.5	-0.0	2.1	-0.1
SD	2.37	1.93	1.54	0.72	2.00	1.12
ItchRO(Obs) 4-Week Average Morning Score						
n	8	8	23	23	31	31
Mean	1.5	-0.8	1.6	-0.7	1.6	-0.7
SD	0.54	0.83	0.92	0.59	0.83	0.65

ItchRO(Pt) 4-Week Average Morning Score						
n	2	2	7	7	9	9
Mean	1.2	-0.4	1.4	-0.7	1.4	-0.6
SD	0.27	0.65	1.03	0.57	0.90	0.57
Median	1.19	-0.38	1.26	-0.81	1.26	-0.81

Source: Appendix 8.1, Table 14.2.6.1.1, Table 14.2.7.1.1, Table 14.2.8.1.1, Table 14.2.9.1.1, Table 14.2.10.1.1
Abbreviations: CFB = change from baseline, defined as post-baseline value minus baseline value; ET = early termination; ItchRO(Obs) = Itch Reported Outcome (Observer); ItchRO(Pt) = Itch Reported Outcome (Patient); n = number in a given category; PFIC = progressive familial intrahepatic cholestasis; SD = standard deviation
Note: The Week 13/ET time point represents the last post-baseline value obtained within 7 days of the last dose prior to the Week 13 visit. Children at least 9 years of age completed the patient instrument ItchRO(Pt). Children between the ages of 5 and 8 years of age completed the ItchRO(Pt) with the assistance of their caregiver. There is no ItchRO(Pt) report for participants under the age of 5.

5.1.3. Other Efficacy Endpoints Evaluations

Table 5-3 summarizes sBA levels during the 72-week observation period. Table 5-4 summarizes the changes from baseline to Week 72/ET in sBA, ALT, total bilirubin, and direct bilirubin, and the changes from baseline to Week 48/ET in ItchRO(Obs) and ItchRO(Pt), for participants receiving QD dosing.

A numerical increase in sBA concentrations (mean [SD] change from baseline, 22 [84.5] µmol/L) was observed in participants with PFIC1 (Table 5-4). In contrast, a numerical reduction (improvement) was noted in participants with PFIC2 (mean [SD] change from baseline, -10 [162.8] µmol/L). In the overall study population, the mean (SD) change from baseline was -2 (146.0) µmol/L.

A numerical increase in ALT concentrations (mean [SD] change from baseline, 10 [35.3] U/L) was observed in participants with PFIC1. In contrast, a numerical reduction was noted in participants with PFIC2 (mean [SD] change from baseline, -19 [65.0] U/L). In the overall study population, the mean (SD) change from baseline was -12 (59.6) U/L.

Numerical increases in total bilirubin were observed in participants with PFIC1 and PFIC2 (mean [SD] change from baseline, 3.1 [3.69] mg/dL and 0.8 [2.21] mg/dL, respectively). In the overall study population, the mean (SD) change from baseline was 1.4 (2.81) mg/dL.

Numerical increases in direct bilirubin were observed in participants with PFIC1 and PFIC2 (mean [SD] change from baseline, 1.1 [2.12] mg/dL and 0.6 [1.74] mg/dL, respectively). In the overall study population, the mean [SD] change from baseline was 0.7 (1.82) mg/dL.

A smaller numerical reduction from baseline to Week 48/ET in ItchRO(Obs) 4-week average morning score was observed in participants with PFIC1 (mean [SD] change from baseline, -0.7 [0.88] compared to participants with PFIC2 -1.0 [0.96]). In the overall study population, the mean (SD) change from baseline was -0.9 (0.94).

A smaller numerical reduction from baseline to Week 48/ET in ItchRO(Pt) 4-week average morning score was observed in participants with PFIC1 (mean [SD] change from baseline, -0.9 [0.20] compared to participants with PFIC2 (mean [SD] change from

baseline -1.0 [0.80]). In the overall study population, the mean (SD) change from baseline was -1.0 (0.69).

Table 5-3: Serum Bile Acid Level – Change from Baseline Over Time to Week 72 (Modified Intent-to-Treat Population)

	PFIC Type					
	PFIC1		PFIC2		Overall	
Visit Statistic	Observed	CFB	Observed	CFB	Observed	CFB
Serum Bile Acid (µmol/L)						
Baseline						
n	8		23		31	
Mean	262		393		359	
SD	99.6		144.6		145.1	
Week 4						
n	7	7	22	22	29	29
Mean	291	17	333	-59	323	-40
SD	98.0	109.3	206.2	177.9	185.2	165.5
Week 8						
n	8	8	22	22	30	30
Mean	256	-6	362	-29	334	-23
SD	103.8	89.2	206.0	162.4	188.7	145.3
Week 13						
n	8	8	22	22	30	30
Mean	280	18	353	-33	334	-20
SD	100.4	95.7	225.4	180.7	200.8	162.4
Week 24						
n	8	8	21	21	29	29
Mean	242	-20	325	-58	302	-47
SD	95.1	105.4	213.9	185.4	190.8	166.2
Week 36						
n	8	8	21	21	29	29
Mean	249	-12	290	-84	279	-65
SD	100.0	101.0	202.3	181.5	179.1	164.8
Week 48						
n	6	6	20	20	26	26
Mean	344	57	315	-57	322	-30
SD	92.3	92.7	215.6	209.2	192.8	193.3

Visit Statistic	PFIC Type				Overall	
	PFIC1		PFIC2			
	Observed	CFB	Observed	CFB	Observed	CFB
Week 60						
n	6	6	19	19	25	25
Mean	272	18	362	-12	341	-5
SD	100.6	71.9	264.0	232.1	236.5	204.1
Week 72						
n	6	6	17	17	23	23
Mean	277	22	333	-26	318	-14
SD	77.9	99.9	195.3	180.3	172.5	162.5

Source: Appendix 8.1, Table 14.2.4.1.1

Abbreviations: CFB = change from baseline, defined as post-baseline value minus baseline value; n = number in a given category; PFIC = progressive familial intrahepatic cholestasis; SD = standard deviation

Table 5-4: Exploratory Efficacy Endpoints: Change from Baseline to Endpoint (Week 72/ET or Week 48/ET) (Modified Intent-to-Treat Population)

	PFIC Type					
	PFIC1		PFIC2		Overall	
Statistic Endpoint	Observed	CFB	Observed	CFB	Observed	CFB
Serum Bile Acid (µmol/L) Week 72/ET						
n	8	8	23	23	31	31
Mean	284	22	383	-10	357	-2
SD	84.5	84.5	212.8	162.8	191.8	146.0
Alanine Aminotransferase (U/L) Week 72/ET						
n	8	8	23	23	31	31
Mean	66	10	107	-19	96	-12
SD	31.1	35.3	101.3	65.0	89.9	59.6
Total Bilirubin (mg/dL) Week 72/ET						
n	8	8	23	23	31	31
Mean	8.6	3.1	2.8	0.8	4.3	1.4
SD	7.60	3.69	3.07	2.21	5.19	2.81
Direct Bilirubin (mg/dL) Week 72/ET						
n	8	8	23	23	31	31
Mean	5.1	1.1	2.1	0.6	2.9	0.7
SD	3.78	2.12	2.43	1.74	3.07	1.82

ItchRO(Obs)						
4-Week Average Morning Score Week 48/ET						
n	7	7	21	21	28	28
Mean	1.5	-0.7	1.2	-1.0	1.2	-0.9
(95% CI for Mean)	(0.682 2.343)	(-1.464 0.158)	(0.745 1.577)	(-1.461 -0.585)	(0.897 1.601)	(-1.295 -0.566)
SD	0.90	0.88	0.91	0.96	0.91	0.94
Median	1.450	-0.510	1.192	-0.965	1.254	-0.940
Min, Max	0.15, 3.00	-2.29, 0.46	0.00, 2.63	-3.05, 0.67	0.00, 3.00	-3.05, 0.67
ItchRO(Pt)						
4-Week Average Morning Score Week 48/ET						
n	2	2	6	6	8	8
Mean	0.6	-0.9	0.8	-1.0	0.8	-1.0
(95% CI for Mean)	(-1.022 2.282)	(-2.733 0.851)	(-0.029 1.705)	(-1.848 -0.159)	(0.194 1.378)	(-1.561 -0.415)
SD	0.18	0.20	0.83	0.80	0.70	0.69
Median	0.630	-0.941	0.569	-0.935	0.630	-0.935
Min, Max	0.50, 0.76	-1.08, -0.80	0.10, 1.96	-1.98, -0.13	0.10, 1.96	-1.98, -0.13

Source: Appendix 8.1, Table 14.2.4.1.1, Table 14.2.6.1.1, Table 14.2.7.1.1, Table 14.2.8.1.1, Table 14.2.9.1.1, Table 14.2.10.1.1

Abbreviations: CFB = change from baseline, defined as post-baseline value minus baseline value; CI = confidence interval; ET = early termination; ItchRO(Obs) = Itch Reported Outcome (Observer); ItchRO(Pt) = Itch Reported Outcome (Patient); Max = maximum; Min = minimum; n = number in a given category; PFIC = progressive familial intrahepatic cholestasis; SD = standard deviation

Note: For direct bilirubin concentrations reported as below the minimum quantitation limit, half of the minimum quantitation limit is used as the analysis value. For concentrations reported as above the maximum quantitation limit, the maximum quantitation limit is used as the analysis value. The Week 48/ET time point represents the last post-baseline value obtained within 7 days of the last dose prior to the Week 48 visit. The Week 72 time point represents the last post-baseline value obtained within 7 days of the last dose prior to the Week 72 visit. Children at least 9 years of age completed the patient instrument ItchRO (Pt). Children between the ages of 5 and 8 years of age completed the ItchRO (Pt) with the assistance of their caregiver. There is no ItchRO (Pt) report for participants under the age of 5.

5.1.4. Posthoc Analysis

Table 5-5 summarizes the changes from baseline to Week 72/ET in multiparameter responders as defined by a) at least 70% reduction or normalization of sBA and b) reduction of 1.0 or score <1.0 in ItchRO(Obs).

This responder analysis showed improvements beyond sBA and ItchRO(Obs) in AST, ALT and total bilirubin in those participants who had elevated values at baseline.

Table 5-5: Posthoc Analysis: Non-truncating PFIC2 (BSEP deficient) Multiparameter Responders

Participant ID	Measure	Values									
		BL	Wk2	Wk4	Wk8	Wk13	Wk24[a]	Wk36	Wk48	Wk60	Wk72
001054	sBA	142.2	41.7[b]	24.7[b]	12.8[b]	5.8[b]	1.1[b]	0.7[b]	1.1[b]	2.2[b]	4.6[b]
	% change from BL		*-71%*	*-83%*	*-91%*	*-96%*	*-99%*	*-99.5%*	*-99%*	*-98%*	*-97%*
	ItchRO(Obs)	1.93	NA	1.29	**0.93[c]**	**0.50[c]**	**0.00[c]**	NA	**0.00[c]**	NA	NA
	% change from BL		*NA*	*-33%*	*-52%*	*-74%*	*-100%*	*NA*	*-100%*	*NA*	*NA*
	ALT	88	89	89	69	42	18	16	15	16	13
	% change from BL		*+1%*	*+1%*	*-22%*	*-52%*	*-80%*	*-82%*	*-83%*	*-82%*	*-85%*
	AST	110	100	88	76	52	33	37	28	32	26
	% change from BL		*-9%*	*-20%*	*-31%*	*-53%*	*-70%*	*-66%*	*-75%*	*-71%*	*-76%*
	Total bilirubin	1.9	1.7	1.5	0.8	0.3	0.1	0.2	0.2	0.2	0.1
	% change from BL		*-11%*	*-21%*	*-58%*	*-84%*	*-95%*	*-89%*	*-89%*	*-89%*	*-95%*

Participant ID	Measure	Values									
		BL	Wk2	Wk4	Wk8	Wk13	Wk24[a]	Wk36	Wk48	Wk60	Wk72
016051	sBA	442.4	276.1	21.7[b]	1.9[b]	1.0[b]	1.5[b]	3.0[b]	2.0[b]	1.8[b]	1.2[b]
	% change from BL		*-38%*	*-95%*	*-99.6%*	*-99.8%*	*-99.7%*	*-99%*	*-99.6%*	*-99.6%*	*-99.7%*
	ItchRO(Obs)	3.29	NA	2.93	3.00	**1.43[c]**	**1.00[c]**	NA	**1.00[c]**	NA	NA
	% change from BL		*NA*	*-11%*	*-9%*	*-57%*	*-70%*	*NA*	*-70%*	*NA*	*NA*
	ALT	111	141	89	35	20	19	32	16	18	14
	% change from BL		*+27%*	*-20%*	*-68%*	*-82%*	*-83%*	*-71%*	*-86%*	*-84%*	*-87%*
	AST	92	91	64	36	28	34	42	25	27	33
	% change from BL		*-1%*	*-30%*	*-61%*	*-70%*	*-63%*	*-54%*	*-73%*	*-71%*	*-64%*
	Total bilirubin	0.4	0.4	0.4	0.2	0.3	0.3	0.4	0.5	0.5	0.2
	% change from BL		*0%*	*0%*	*-50%*	*-25%*	*-25%*	*0%*	*+25%*	*+25%*	*-50%*
016052	sBA	104.1	1.1[b]	3.1[b]	2.6[b]	3.0[b]	2.7[b]	6.0[b]	3.1[b]	3.8[b]	3.7[b]
	% change from BL		*-99%*	*-97%*	*-98%*	*-97%*	*-97%*	*-94%*	*-97%*	*-96%*	*-96%*
	ItchRO(Obs)	2.50	NA	1.57	**1.21[c]**	**1.00[c]**	**1.00[c]**	NA	**1.00[c]**	NA	NA
	% change from BL		*NA*	*-37%*	*-52%*	*-60%*	*-60%*	*NA*	*-60%*	*NA*	*NA*
	ALT	14	12	21	20	16	12	15	13	12	16
	% change from BL		*-14%*	*+50%*	*+43%*	*+14%*	*-14%*	*+7%*	*-7%*	*-14%*	*+14%*
	AST	28	27	30	34	32	27	31	30	27	31
	% change from BL		*-4%*	*+7%*	*+21%*	*+14%*	*-4%*	*+11%*	*+7%*	*-4%*	*+11%*
	Total bilirubin	0.1	0.1	0.2	0.2	0.2	0.2	0.3	0.3	0.2	0.4
	% change from BL		*0%*	*+100%*	*+100%*	*+100%*	*+100%*	*+200%*	*+200%*	*+100%*	*+300%*

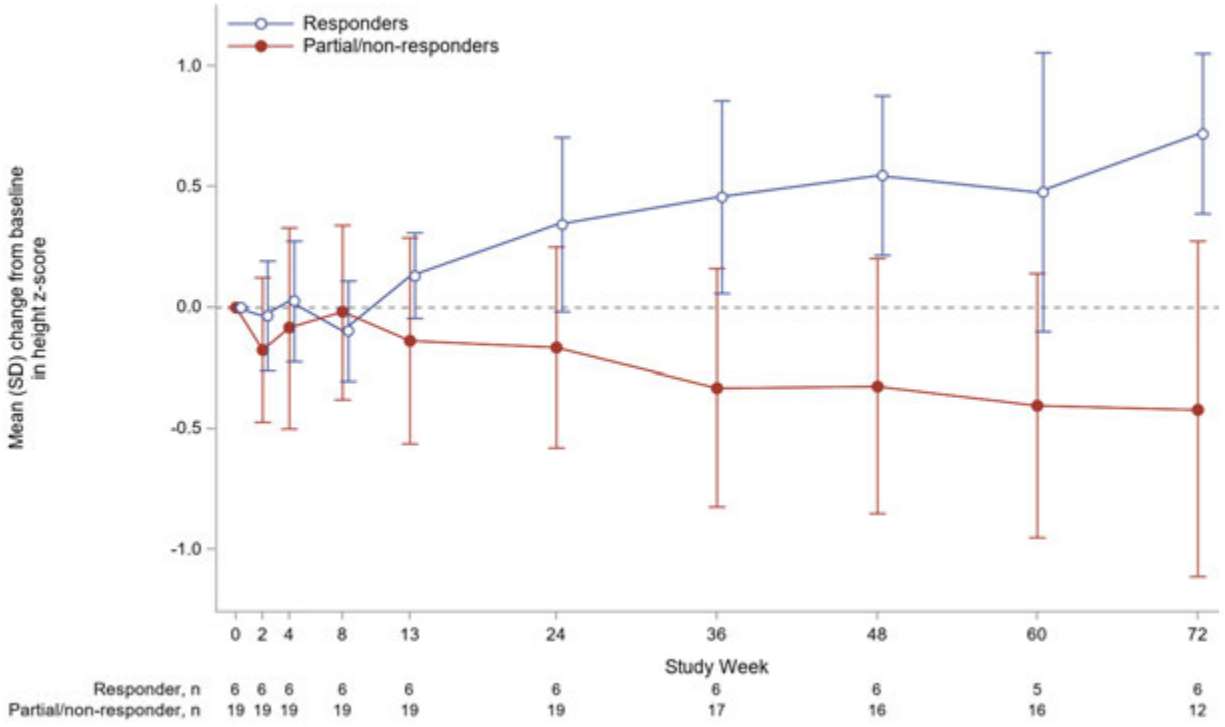
Participant ID	Measure	Values									
		BL	Wk2	Wk4	Wk8	Wk13	Wk24[a]	Wk36	Wk48	Wk60	Wk72
016053	sBA	541.1	438.8	28.2[b]	77.7[b]	78.3[b]	52.7[b]	35.4[b]	19.1[b]	71.8[b]	276.2
	% change from BL		*-19%*	*-95%*	*-86%*	*-86%*	*-90%*	*-93%*	*-96%*	*-87%*	*-49%*
	ItchRO(Obs)	3.14	NA	2.43	**1.64[c]**	**1.43[c]**	**0.64[c]**	NA	**0.00[c]**	NA	NA
	% change from BL		*NA*	*-23%*	*-48%*	*-54%*	*-80%*	*NA*	*-100%*	*NA*	*NA*
	ALT	24	30	33	15	13	12	12	12	15	25
	% change from BL		*+25%*	*+38%*	*-38%*	*-46%*	*-50%*	*-50%*	*-50%*	*-38%*	*+4%*
	AST	40	40	33	25	28	28	29	27	35	32
	% change from BL		*0%*	*-18%*	*-38%*	*-30%*	*-30%*	*-28%*	*-33%*	*-13%*	*-20%*
	Total bilirubin	0.6	0.8	0.4	0.6	0.8	0.5	1.2	0.7	0.5	0.6
	% change from BL		*+33%*	*-33%*	*0%*	*+33%*	*-17%*	*+100%*	*+17%*	*-17%*	*0%*
027051	sBA	34.3	35.8	2.4[b]	1.2[b]	2.5[b]	3.0[b]	9.2[b]	22.5	3.0[b]	68.3
	% change from BL		*+4%*	*-93%*	*-97%*	*-93%*	*-91%*	*-73%*	*-34%*	*-91%*	*+99%*
	ItchRO(Obs)	1.64	NA	**0.71[c]**	**0.50[c]**	**0.29[c]**	**0.57[c]**	NA	**0.57[c]**	NA	NA
	% change from BL		*NA*	*-57%*	*-70%*	*-82%*	*-65%*	*NA*	*-65%*	*NA*	*NA*
	ALT	13	12	11	13	12	20	10	12	13	12
	% change from BL		*-8%*	*-15%*	*0%*	*-8%*	*+54%*	*-23%*	*-8%*	*0%*	*-8%*
	AST	39	37	34	37	38	42	39	44	38	32
	% change from BL		*-5%*	*-13%*	*-5%*	*-3%*	*+8%*	*0%*	*+13%*	*-3%*	*-18%*
	Total bilirubin	0.3	0.4	0.2	0.2	0.3	0.1	0.2	0.1	0.3	0.2
	% change from BL		*+33%*	*-33%*	*-33%*	*0%*	*-67%*	*-33%*	*-67%*	*0%*	*-33%*

Participant ID	Measure	Values									
		BL	Wk2	Wk4	Wk8	Wk13	Wk24[a]	Wk36	Wk48	Wk60	Wk72
080051	sBA	425.6	237.8	104.5[b]	295.6	106.5[b]	60.1[b]	93.2[b]	51.5[b]	6.7[b]	131.5
	% change from BL		*-44%*	*-75%*	*-31%*	*-75%*	*-86%*	*-78%*	*-88%*	*-98%*	*-69%*
	ItchRO(Obs)	2.79	NA	**1.00[c]**	**1.57[c]**	**1.71[c]**	**1.79[c]**	NA	**1.36[c]**	NA	NA
	% change from BL		*NA*	*-64%*	*-44%*	*-39%*	*-36%*	*NA*	*-51%*	*NA*	*NA*
	ALT	63	72	63	73	52	44	45	76	47	32
	% change from BL		*+14%*	*0%*	*+16%*	*-17%*	*-30%*	*-29%*	*+21%*	*-25%*	*-49%*
	AST	61	61	64	60	52	49	48	64	51	39
	% change from BL		*0%*	*+5%*	*-2%*	*-15%*	*-20%*	*-21%*	*+5%*	*-16%*	*-36%*
	Total bilirubin	0.3	0.3	0.3	0.2	0.2	0.2	0.3	0.2	0.3	0.3
	% change from BL		*0%*	*0%*	*-33%*	*-33%*	*-33%*	*0%*	*-33%*	*0%*	*0%*

Source: Table provided by Mirum Pharmaceuticals, Inc., using data from Appendix 8.2, Listing 16.1.1 (see Appendix 8.1.4, Table 14.4.1)
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BL = baseline; BSEP = bile salt exporter protein; ID = identification; ItchRO(Obs) = Itch Reported Outcome (Observer); NA = not applicable (% not calculated since value was missing); PFIC = progressive familial intrahepatic cholestasis; sBA = serum bile acid; Wk = week.
a ItchRO(Obs) was collected for 4 weeks following Week 24 and is reported as Week 28 in outputs.
b Gray shaded table cells: at least 70% reduction from baseline in sBA.
c Bolded ItchRO (Obs) values: At least 1.0 reduction from baseline in ItchRO(Obs).
Note: data values for % change from baseline can be provided by Mirum Pharmaceuticals, Inc upon request.

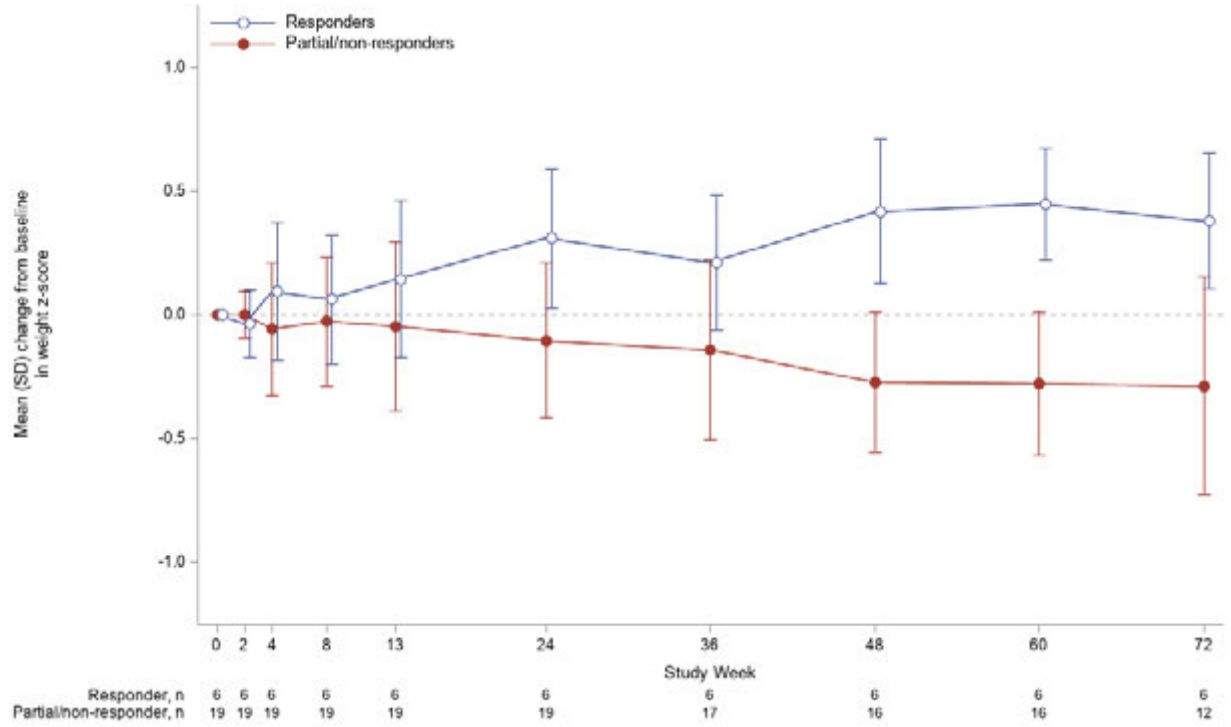
Figure 5-1 and Figure 5-2 summarize the height and weight z-scores in the 6 nt-PFIC2 participants that exhibited a multiparameter response compared to PFIC2 participants that did not exhibit a multiparameter response.

Figure 5-1: Posthoc Analysis: Change from Baseline in Height z-score Over Time in Responders vs. Partial/Non-responders



Source: Figure provided by Mirum Pharmaceuticals, Inc., using data from Appendix 8.2, Listing 16.2.7.7 (see Appendix 8.1.4, Figure 14.4.1)
Abbreviation: n = number in a given category; SD = standard deviation
Note: mean (SD) data values can be provided by Mirum Pharmaceuticals, Inc. upon request.

Figure 5-2: Posthoc Analysis: Change from Baseline in Weight z-score Over Time in Responders vs. Partial/Non-responders



Source: Figure provided by Mirum Pharmaceuticals, Inc., using data from Appendix 8.2, Listing 16.2.7.7 (see Appendix 8.1.4, Figure 14.4.2)
Abbreviation: n = number in a given category; SD = standard deviation
Note: mean (SD) data values can be provided by Mirum Pharmaceuticals, Inc. upon request.

5.2. SAFETY

5.2.1. Adverse Events

5.2.1.1. Brief Summary of Adverse Events

Table 5-6 presents an overview of the occurrence of TEAEs in the Safety Population during the 72-week observation period. No deaths were reported during the conduct of the study. All participants experienced at least 1 TEAE. 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%]). Serious TEAEs were experienced by 14 participants (42.4%) overall, including 4 participants (50.0%) with PFIC1 and 10 participants (40.0%) with PFIC2. Serious TEAEs 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%]). Treatment-emergent AEs leading to study drug discontinuation were experienced by 5 participants (15.2%) overall; all were participants with PFIC2.

Table 5-6: Summary of Treatment-emergent Adverse Events During the 72-Week Observation Period (Safety Population)

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
PFIC Type: PFIC1	
Participants with at Least 1	
TEAE	8 (100.0)
TEAE Potentially Related to Study Drug[a]	3 (37.5)
Serious TEAE	4 (50.0)
Serious TEAE Potentially Related to Study Drug[a]	1 (12.5)
TEAE Leading to Study Drug Discontinuation	0
TEAE Leading to Death	0

Category	Weeks 0-72 (Days 1-504) (N=33) n (%)
PFIC Type: PFIC2	
Participants with at Least 1	
TEAE	25 (100.0)
TEAE Potentially Related to Study Drug[a]	20 (80.0)
Serious TEAE	10 (40.0)
Serious TEAE Potentially Related to Study Drug[a]	4 (16.0)
TEAE Leading to Study Drug Discontinuation	5 (20.0)
TEAE Leading to Death	0

Source: Appendix 8.1, Table 14.3.2.1
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.

5.2.1.2. Analyses of All Adverse Events

5.2.1.2.1. Frequency of AEs by Preferred Term

Table 5-7 displays the TEAEs that were reported in 3 or more participants. The most frequently reported TEAEs were in the infections and infestations SOC, followed by the GI disorders SOC, general disorders and administration site conditions SOC, and respiratory, thoracic and mediastinal disorders SOC (Appendix 8.1, Table 14.3.2.2). 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%]).

Table 5-7: Incidence of Treatment-emergent Adverse Events in 3 or More of Participants During the 72-Week observation period (Safety Population)

System Organ Class[a] Preferred Term	Weeks 0-72 (Days 1-504) (N=33) n (%)
Number of Participants with at Least 1 TEAE	33 (100.0)
Ear and labyrinth disorders	4 (12.1)
Ear pain	3 (9.1)

System Organ Class[a] Preferred Term	Weeks 0-72 (Days 1-504) (N=33) n (%)
Gastrointestinal disorders	28 (84.8)
Diarrhoea	16 (48.5)
Vomiting	13 (39.4)
Abdominal pain	9 (27.3)
Abdominal pain upper	6 (18.2)
Faeces pale	5 (15.2)
Constipation	5 (15.2)
Frequent bowel movements	4 (12.1)
Toothache	3 (9.1)
General disorders and administration site conditions	26 (78.8)
Pyrexia	17 (51.5)
Irritability	4 (12.1)
Disease progression	3 (9.1)
Fatigue	3 (9.1)
Influenza like illness	3 (9.1)
Malaise	3 (9.1)
Hepatobiliary disorders	8 (24.2)
Hyperbilirubinaemia	3 (9.1)
Infections and infestations	29 (87.9)
Nasopharyngitis	8 (24.2)
Upper respiratory tract infection	6 (18.2)
Gastroenteritis	4 (12.1)
Pharyngitis streptococcal	3 (9.1)
Viral infection	3 (9.1)
Injury, poisoning and procedural complications	11 (33.3)
Traumatic haemorrhage	3 (9.1)
Investigations	12 (36.4)
International normalised ratio increased	7 (21.2)
Blood bilirubin increased	4 (12.1)
Metabolism and nutrition disorders	11 (33.3)
Decreased appetite	3 (9.1)
Vitamin D deficiency	3 (9.1)
Musculoskeletal and connective tissue disorders	7 (21.2)
Pain in extremity	3 (9.1)
Respiratory, thoracic and mediastinal disorders	21 (63.6)
Cough	13 (39.4)
Oropharyngeal pain	7 (21.2)
Epistaxis	8 (24.2)

System Organ Class[a] Preferred Term	Weeks 0-72 (Days 1-504) (N=33) n (%)
Skin and subcutaneous tissue disorders	14 (42.4)
Pruritus	8 (24.2)
Rash	4 (12.1)

Source: Appendix 8.1, Table 14.3.2.2

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

a Adverse events were coded using MedDRA version 16.0.

Note: Percentages are 100*n/N. Participants were counted only once for each System Organ Class and Preferred Term. 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.

5.2.1.2.2. Adverse Events by Severity

Most of the reported TEAEs were mild or moderate in severity. No events of Grade 5 (fatal) severity were reported. 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 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 (Appendix 8.1, Table 14.3.2.3 and Table 14.3.2.5). Table 5-8 provides a summary of TEAEs that were considered severe (CTCAE Grade 3). 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).

Table 5-8: Incidence of CTCAE Grade 3 Treatment-emergent Adverse Events During the 72-Week Observation Period

System Organ Class[a] Preferred Term[b]	Weeks 0-72 (Days 1-504) (N=33) n (%)
Any System Organ Class	
Any Event (Total)	33 (100.0)
Grade 1 (Mild)	8 (24.2)
Grade 2 (Moderate)	12 (36.4)
Grade 3 (Severe)	11 (33.3)
Grade 4 (Life-threatening)	2 (6.1)
Grade 5 (Fatal)	0
Gastrointestinal disorders	
Diarrhoea	2 (6.1)
Abdominal pain	1 (3.0)
Diarrhoea haemorrhagic	1 (3.0)
Pancreatic insufficiency	1 (3.0)
Pancreatitis	1 (3.0)
General disorders and administration site conditions	
Irritability	1 (3.0)
Disease progression	2 (6.1)
Hepatobiliary disorders	
Hyperbilirubinaemia	1 (3.0)
Injury, poisoning and procedural complications	
Upper limb fracture	1 (3.0)
Investigations	
Blood bilirubin increased	3 (9.1)
Bilirubin conjugated increased	1 (3.0)
Metabolism and nutrition disorders	
Iron deficiency	1 (3.0)
Malnutrition	1 (3.0)
Nervous system disorders	
Convulsion	1 (3.0)
Encephalopathy	1 (3.0)

System Organ Class[a] Preferred Term[b]	Weeks 0-72 (Days 1-504) (N=33) n (%)
Skin and subcutaneous tissue disorders	
Pruritus	2 (6.1)

Source: Appendix 8.2, Listing 16.2.7.1

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; n = number in a given category; N = number of participants; PFIC = progressive familial intrahepatic cholestasis; TEAE = treatment-emergent adverse event

a Adverse events were coded using MedDRA version 16.0.

b Severity grades are reported according to the CTCAE version 4.0. If the CTCAE does not have a grading for a particular adverse event, the severity of the event is reported by the investigator as mild, moderate, or severe.

Note: Percentages are 100*n/N. A participant with multiple events per System Organ Class or per Preferred Term is counted only once at the maximum reported severity grade. 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.

5.2.1.2.3. Treatment-related Adverse Events

Any TEAE determined to be possibly related or related by the investigator was categorized as related to study drug. Table 5-9 displays TEAEs judged to be potentially related to study treatment that were reported in 2 or more participants during the 72-week observation period. Treatment-related TEAEs were experienced by 23 participants (69.7%) during the 72-week observation period.

Gastrointestinal events 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%]). Other frequently reported preferred terms included the following: INR increased (5 participants [(15.2%]); and irritability, hyperbilirubinemia, vitamin E decreased, INR abnormal, decreased appetite, vitamin D deficiency, and pruritus (2 participants [6.1%] each). The remaining treatment-related TEAEs were reported by no more than 1 participant each.

Table 5-9: Incidence of Treatment-Related Treatment-emergent Adverse Events in 2 or More of Participants During the 72-Week Observation Period (Safety Population)

System Organ Class[a] Preferred Term	Weeks 0-72 (Days 1-504) (N=33) n (%)
Number of Participants with at Least 1 Treatment-related TEAE	23 (69.7)
Gastrointestinal disorders	18 (54.5)
Diarrhoea	10 (30.3)
Abdominal pain	7 (21.2)
Abdominal pain upper	6 (18.2)
Vomiting	5 (15.2)
Frequent bowel movements	4 (12.1)
Faeces pale	2 (6.1)
General disorders and administration site conditions	2 (6.1)
Irritability	2 (6.1)
Hepatobiliary disorders	2 (6.1)
Hyperbilirubinaemia	2 (6.1)
Investigations	6 (18.2)
International normalised ratio increased	5 (15.2)
Vitamin E decreased	2 (6.1)
International normalised ratio abnormal	2 (6.1)
Metabolism and nutrition disorders	4 (12.1)
Decreased appetite	2 (6.1)
Vitamin D deficiency	2 (6.1)
Skin and subcutaneous tissue disorders	2 (6.1)
Pruritus	2 (6.1)

Source: Appendix 8.1, Table 14.3.2.4

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

a Adverse events were coded using MedDRA version 16.0.

Note: Percentages are 100*n/N. Participants were counted only once for each System Organ Class and Preferred Term. 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.

5.2.1.3. Deaths

No deaths were reported during the conduct of this study (Appendix 8.1, Table 14.3.2.15).

5.2.1.4. Serious Adverse Events

Narratives for participants who had a treatment-emergent SAE during the 72-week observation period are provided in Appendix 10.

Table 5-10 provides a summary of SAEs during the 72-week observation period. Serious AEs were experienced by 14 participants (42.4%) during the 72-week observation period. Gastrointestinal events 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%).

Table 5-10: Incidence of Treatment-emergent Serious Adverse Events During the 72-Week Observation Period (Safety Population)

System Organ Class[a] Preferred Term	Weeks 0-72 (Days 1-504) (N=33) n (%)
Number of Participants with at Least 1 Serious TEAE	14 (42.4)
Gastrointestinal disorders	6 (18.2)
Abdominal pain	2 (6.1)
Diarrhoea	2 (6.1)
Abdominal pain upper	1 (3.0)
Melaena	1 (3.0)
Pancreatitis	1 (3.0)
General disorders and administration site conditions	1 (3.0)
Disease progression	1 (3.0)
Hepatobiliary disorders	1 (3.0)
Cholelithiasis	1 (3.0)
Infections and infestations	3 (9.1)
Gastroenteritis	1 (3.0)
Respiratory tract infection	1 (3.0)
Viral infection	1 (3.0)
Injury, poisoning and procedural complications	2 (6.1)
Radius fracture	1 (3.0)
Ulna fracture	1 (3.0)
Upper limb fracture	1 (3.0)
Investigations	2 (6.1)
Blood bilirubin increased	1 (3.0)
International normalised ratio increased	1 (3.0)

System Organ Class[a] Preferred Term	Weeks 0-72 (Days 1-504) (N=33) n (%)
Metabolism and nutrition disorders	1 (3.0)
Electrolyte imbalance	1 (3.0)
Hypocalcaemia	1 (3.0)
Respiratory, thoracic and mediastinal disorders	1 (3.0)
Dyspnoea	1 (3.0)
Skin and subcutaneous tissue disorders	1 (3.0)
Pruritus	1 (3.0)
Surgical and medical procedures	1 (3.0)
Enteral nutrition	1 (3.0)
Gastrointestinal tube insertion	1 (3.0)

Source: Appendix 8.1, Table 14.3.2.6
Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; n = number in a given category; N = number of participants; PFIC = progressive familial intrahepatic cholestasis; TEAE = treatment-emergent adverse event
a Adverse events were coded using MedDRA version 16.0.
Note: Percentages are 100*n/N. Participants were counted only once for each System Organ Class and Preferred Term. 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.

Table 5-11 provides a summary of SAEs judged to be potentially related to study treatment during the 72-week observation period. 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. Each of the treatment-related SAEs required hospitalization with the exception of blood bilirubin increased (Appendix 8.2, Listing 16.2.2.2).

Table 5-11: Incidence of Treatment-related Treatment-emergent Serious Adverse Events During the 72-Week Observation Period (Safety Population)

System Organ Class[a] Preferred Term	Weeks 0-72 (Days 1-504) (N=33) n (%)
Number of Participants with at Least 1 Treatment-related SAE	5 (15.2%)
Gastrointestinal disorders	3 (9.1%)
Abdominal pain	1 (3.0%)
Abdominal pain upper	1 (3.0%)
Diarrhoea	1 (3.0%)
Pancreatitis	1 (3.0%)
Investigations	2 (6.1%)
Blood bilirubin increased	1 (3.0%)
International normalised ratio increased	1 (3.0%)

Source: Appendix 8.1, Table 14.3.2.7

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; n = number in a given category; N = number of participants; PFIC = progressive familial intrahepatic cholestasis; SAE = serious adverse event; TEAE = treatment-emergent adverse event

a Adverse events were coded using MedDRA version 16.0.

Note: Percentages are 100*n/N. Participants were counted only once for each System Organ Class and Preferred Term. 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.

5.2.1.5. Discontinuations and/or Dose Modifications Due to Adverse Events

Narratives for participants who had AEs that resulted in permanent treatment discontinuation during the 72-week observation period are provided in Appendix 10.

Treatment-emergent AEs that resulted in permanent treatment discontinuation during the 72-week observation period are presented in Table 5-12. A total of 5 participants (15.2%) experienced TEAEs that led to permanent treatment discontinuation. One TEAE (pancreatitis) that led to permanent treatment discontinuation was considered as potentially related to study drug (i.e., determined by the investigator to be possibly related or related) (Appendix 8.2, Listing 16.2.7.4). The other TEAEs were considered unlikely related to study drug (i.e., determined by the investigator to be not related or unlikely/remotely related). The TEAEs that led to permanent treatment discontinuation included disease progression (2 participants [6.1%]; both not related), blood bilirubin increased (2 participants [6.1%]; 1 not related and 1 unlikely/remotely related), and pancreatitis (1 participant [3.0%]; possibly related). All of the TEAEs that led to permanent treatment discontinuation were experienced by participants with PFIC2 (Appendix 8.1, Table 14.3.2.8).

Table 5-12: Incidence of Adverse Events Leading to Permanent Treatment Discontinuation During the 72-Week Observation Period (Safety Population)

System Organ Class[a] Preferred Term	Weeks 0-72 (Days 1-504) (N=33) n (%)
Number of Participants with at Least 1 TEAE Leading to Permanent Treatment Discontinuation	5 (15.2)
Gastrointestinal disorders	1 (3.0)
Pancreatitis	1 (3.0)
General disorders and administration site conditions	2 (6.1)
Disease progression	2 (6.1)
Investigations	2 (6.1)
Blood bilirubin increased	2 (6.1)

Source: Appendix 8.1, Table 14.3.2.8

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

a Adverse events were coded using MedDRA version 16.0.

Note: Percentages are 100*n/N. Participants were counted only once for each System Organ Class and Preferred Term. 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.

5.2.1.6. Adverse Events of Special Interest

5.2.1.6.1. Gastrointestinal Events

Table 5-13 provides an overview of the occurrence of TEAEs of special interest during the 72-weeks observation period. A total of 27 participants (81.8%) experienced TEAEs of special interest in the GI disorders SOC. The most frequently reported event was diarrhea (16 participants [48.5%]), followed by vomiting (13 participants [39.4%]), abdominal pain (9 participants [27.3%], and abdominal pain upper (6 participants [18.2%]).

Table 5-13: Incidence of Treatment-emergent Adverse Events of Special Interest – Gastrointestinal-related Events During the 72-Week Observation Period (Safety Population)

System Organ Class[a] Preferred Term	Weeks 0-72 (Days 1-504) (N=33) n (%)
Number of Participants with at Least 1 TEAE	27 (81.8)
Gastrointestinal disorders	27 (81.8)
Diarrhoea	16 (48.5)
Vomiting	13 (39.4)
Abdominal pain	9 (27.3)
Abdominal pain upper	6 (18.2)
Faeces pale	5 (15.2)
Frequent bowel movements	4 (12.1)
Abdominal discomfort	1 (3.0)
Gastrointestinal pain	2 (6.1)
Diarrhoea haemorrhagic	1 (3.0)
Faeces discoloured	1 (3.0)
Flatulence	1 (3.0)

Source: Appendix 8.1, Table 14.3.2.9

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

a Adverse events were coded using MedDRA version 16.0.

Note: Percentages are 100*n/N. Participants were counted only once for each System Organ Class and Preferred Term. 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.

5.2.1.6.2. Events Related to Liver Deterioration

A summary of the occurrence of conditions potentially associated with liver deterioration that were experienced by at least 2 participants during the 72-week observation period is presented in Table 5-14. A total of 31 participants (93.9%) experienced TEAEs of special interest that were conditions potentially associated with liver deterioration. The most frequently reported events were in the GI SOC, including diarrhea, vomiting, abdominal pain, and abdominal pain upper (also see Section 5.2.1.6.1).

Table 5-14: Incidence of Treatment-emergent Adverse Events of Special Interest That Were Experienced by at Least 2 Participants – Conditions Associated with Liver Deterioration During the 72-Week Observation Period (Safety Population)

System Organ Class[a, b] Preferred Term	Weeks 0-72 (Days 1-504) (N=33) n (%)
Number of Participants with at Least 1 TEAE	31 (93.9)
Gastrointestinal disorders	28 (84.8)
Diarrhoea	16 (48.5)
Vomiting	13 (39.4)
Abdominal pain	9 (27.3)
Abdominal pain upper	6 (18.2)
Faeces pale	5 (15.2)
Constipation	5 (15.2)
Frequent bowel movements	4 (12.1)
Toothache	3 (9.1)
Gastrointestinal pain	2 (6.1)
Teething	2 (6.1)
Hepatobiliary disorders	8 (24.2)
Hyperbilirubinaemia	3 (9.1)
Jaundice	2 (6.1)
Metabolism and nutrition disorders	11 (33.3)
Decreased appetite	3 (9.1)
Hypocalcaemia	2 (6.1)
Vitamin D deficiency	3 (9.1)
Electrolyte imbalance	2 (6.1)
Skin and subcutaneous tissue disorders	8 (24.2)
Pruritus	8 (24.2)

Source: Appendix 8.1, Table 14.3.2.10

Abbreviations: AE = adverse event; GI = gastrointestinal; MedDRA = Medical Dictionary for Regulatory Activities; n = number in a given category; N = number of participants; PFIC = progressive familial intrahepatic cholestasis; TEAE = treatment-emergent adverse event

a Adverse events were coded using MedDRA version 16.0.

b System Organ Classes associated with liver deterioration included the following: blood and lymphatic system disorders, cardiac disorders, GI disorders, hepatobiliary disorders, metabolism and nutrition disorders, neoplasms benign, malignant and unspecified (incl cysts and polyps), and vascular haemorrhagic disorders. High level terms associated with liver deterioration included the following: spleen disorders, liver and spleen enlargement, gastric and oesophageal haemorrhages, hepatic failure and associated disorders, hepatobiliary signs and symptoms, hepatocellular damage and hepatitis NEC, hepatic and hepatobiliary disorders NEC, hepatobiliary neoplasms NEC, malignant hepatobiliary neoplasms, hepatic neoplasms malignant, hepatobiliary neoplasms malignancy unspecified, hepatobiliary neoplasms malignant NEC, hepatoblastomas, pruritus NEC, gastrointestinal haemorrhages, and portal hypertensions.

Note: Percentages are 100*n/N. Participants were counted only once for each System Organ Class and Preferred Term. 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.

5.2.1.6.3. Fat-soluble Vitamin Deficiency Events

A summary of the occurrence of fat-soluble vitamin deficiency events during the 72-week observation period is presented in Table 5-15.

A total of 18 participants (54.5%) experienced TEAEs of special interest that were fat-soluble vitamin deficiency events. The most frequently reported events included the following: epistaxis (8 participants [24.2%]), INR increased (7 participants [21.2%]), and irritability (4 participants [12.1%]); fatigue and vitamin D deficiency (3 participants [9.1%] each); and vitamin E decreased and INR abnormal (2 participants [6.1%] each). The remaining TEAEs that were fat-soluble vitamin deficiency events were experienced by no more than 1 participant each.

Table 5-15: Incidence of Treatment-emergent Adverse Events of Special Interest – Fat-soluble Vitamin Deficiency Events During the 72-Week Observation Period (Safety Population)

System Organ Class Preferred Term	Weeks 0-72 (Days 1-504) (N=33) n (%)
Number of Participants with at Least 1 TEAE	18 (54.5)
Cardiac disorders	1 (3.0)
Tachycardia	1 (3.0)
Gastrointestinal disorders	2 (6.1)
Haematochezia	1 (3.0)
Melaena	1 (3.0)
General disorders and administration site conditions	7 (21.2)
Irritability	4 (12.1)
Fatigue	3 (9.1)
Investigations	9 (27.3)
International normalised ratio increased	7 (21.2)
Vitamin E decreased	2 (6.1)
International normalised ratio abnormal	2 (6.1)
Platelet count decreased	1 (3.0)
Vitamin D decreased	1 (3.0)
Metabolism and nutrition disorders	3 (9.1)
Vitamin D deficiency	3 (9.1)
Vitamin E deficiency	1 (3.0)

System Organ Class Preferred Term	Weeks 0-72 (Days 1-504) (N=33) n (%)
Musculoskeletal and connective tissue disorders	1 (3.0)
Muscle spasms	1 (3.0)
Psychiatric disorders	1 (3.0)
Anxiety	1 (3.0)
Respiratory, thoracic and mediastinal disorders	8 (24.2)
Epistaxis	8 (24.2)

Source: Appendix 8.1, Table 14.3.2.13

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

a Adverse events were coded using MedDRA version 16.0.

Note: Percentages are 100*n/N. Participants were counted only once for each System Organ Class and Preferred Term. 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.

5.2.2. Clinical Laboratory Evaluation

5.2.2.1. Laboratory Values Over Time

Summaries of clinical laboratory data are provided in Appendix 8.1, Table 14.3.3.1 (clinical chemistry) and Table 14.3.3.2 (hematology). The summaries include mean (SD), median, minimum, and maximum results of clinical chemistry and hematology parameters in the Safety Population by study visit. The changes and percent changes in assessments from baseline to each study visit are also given. Summaries of clinical laboratory data for corrected sodium by study visit are provided in Appendix 8.1, Table 14.3.3.3 (mean [SD], median, minimum, and maximum for observed values and change from baseline), Appendix 8.1, Table 14.3.3.13 (abnormalities), and Appendix 8.1, Table 14.3.3.14 (clinically-meaningful shifts from baseline).

No clinically-meaningful patterns of laboratory abnormalities suggesting safety concerns were identified.

5.2.2.1.1. Fat-soluble Vitamins

Appendix 8.1, Table 14.3.3.3 presents a summary of clinical laboratory data for fat-soluble vitamins including 25-hydroxy vitamin D, alpha tocopherol, alpha tocopherol/total lipids ratio, RBP, retinol:RBP molar ratio, total lipids, and vitamin A. Changes from baseline to endpoint (Week 72/ET) were as follows:

- 25-hydroxy vitamin D: At endpoint (Week 72/ET), a mean (SD) change from baseline value of 0.9 (23.74) ng/mL for the overall study population (-1.4 [32.42] ng/mL and 1.7 [20.77] ng/mL for participants with PFIC1 and PFIC2, respectively)

- Alpha tocopherol: At endpoint (Week 72/ET), a mean (SD) change from baseline value of 0.00 (0.226) mg/dL for participants overall (-0.12 [0.156] mg/dL and 0.04 [0.234] mg/dL for participants with PFIC1 and PFIC2, respectively)
- Alpha tocopherol/total lipids ratio: At endpoint (Week 72/ET), a mean (SD) change from baseline value of -0.03 (0.446) mg/g for participants overall (-0.31 [0.389] mg/g and 0.11 [0.423] mg/g for participants with PFIC1 and PFIC2, respectively)
- Retinol binding protein: At endpoint (Week 72/ET), a mean (SD) change from baseline value of -3.5 (9.11) mg/L for the overall study population (-6.8 [13.36] mg/L and -2.5 [7.24] mg/L for participants with PFIC1 and PFIC2, respectively)
- Retinol:RBP molar ratio: At endpoint (Week 72/ET), a mean (SD) change from baseline value of -0.01 (0.050) mol/mol for the overall study population (-0.00 [0.054] mol/mol and -0.01 [0.049] mol/mol for participants with PFIC1 and PFIC2, respectively)
- Total lipids: At endpoint (Week 72/ET), a mean (SD) change from baseline value of 9.1 (115.48) mg/dL for the overall study population (31.6 [83.22] mg/dL and -2.1 [131.33] mg/dL for participants with PFIC1 and PFIC2, respectively)
- Vitamin A: At endpoint (Week 72/ET), a mean (SD) change from baseline value of -8.5 (18.97) µg/dL for the overall study population (-9.5 [22.27] µg/dL and -8.2 [18.30] µg/dL for participants with PFIC1 and PFIC2, respectively)

The following abnormal results in the category of fat-soluble vitamins were reported as AEs in the investigations SOC during the 72-week observation period (Appendix 8.1, Table 14.3.2.3).

- Vitamin E decreased – reported in 2 participants (6.1%), of Grade 1 severity.
- Vitamin D decreased – reported in 1 participant (3.0%), of Grade 1 severity

The following abnormal results in the category of fat-soluble vitamins were reported as AEs in the metabolism and nutrition disorders SOC (Appendix 8.1, Table 14.3.2.3).

- Vitamin D deficiency – reported in 3 participants (9.1%), of Grade 1 severity
- Vitamin E deficiency – reported in 1 participant (3.0%), of Grade 1 severity

Table 5-16 presents a summary of fat-soluble vitamin level abnormalities in the Safety Population at Week 72/ET. The majority of participants in the overall study population had sufficient 25-hydroxyvitamin D levels (20 participants [60.6%]), sufficient prothrombin INR (22 participants [66.7%]), and sufficient Vitamin A levels (28 participants [84.8%]). The majority of participants in the overall study population had an insufficient alpha tocopherol/total lipids ratio (9 participants [60.0%]) and all participants had an insufficient retinol:RBP molar ratio.

Table 5-16: Summary of Clinical Laboratory Data: Fat-soluble Vitamin Level Abnormalities (Safety Population) during the 72 Week Observation Period

Laboratory Test Timepoint Category	PFIC Type PFIC1 (N=8) n (%)	PFIC Type PFIC2 (N=25) n (%)	Overall (N=33) n (%)
25-Hydroxyvitamin D			
Endpoint (Week 72/ET)	8	25	33
Sufficient (≥20 ng/mL)	6 (75.0)	14 (56.0)	20 (60.6)
Insufficient (<20 ng/mL)	2 (25.0)	10 (40.0)	12 (36.4)
Excess (>96 ng/mL)	0	1 (4.0)	1 (3.0)
Alpha Tocopherol/Total Lipids Ratio[a]			
Endpoint (Week 72/ET)	5	10	15
Sufficient (>0.8 mg/g)	1 (20.0)	5 (50.0)	6 (40.0)
Insufficient (≤0.8 mg/g)	4 (80.0)	5 (50.0)	9 (60.0)
Excess (≥3.5 mg/g)	0	0	0
Prothrombin International Normalized Ratio			
Endpoint (Week 72/ET)	8	25	33
Sufficient (<1.2)	4 (50.0)	18 (72.0)	22 (66.7)
Indeterminate (≥1.2 to 1.5)	4 (50.0)	7 (28.0)	11 (33.3)
Possibly Insufficient (>1.5)	0	0	0
Retinol:RBP Molar Ratio[b]			
Endpoint (Week 72/ET)	8	25	33
Sufficient (≥0.8 mol/mol)	0	0	0
Insufficient (<0.8 mol/mol)	8 (100.0)	25 (100.0)	33 (100.0)
Vitamin A			
Endpoint (Week 72/ET)	8	25	33
Sufficient (20 to 77 µg/dL)	6 (75.0)	22 (88.0)	28 (84.8)
Insufficient (<20 µg/dL)	0	2 (8.0)	2 (6.1)
Excess (>77 µg/dL)	2 (25.0)	1 (4.0)	3 (9.1)

Source: Appendix 8.1, Table 14.3.3.13

Abbreviations: ET = early termination; n = number in a given category; N = number of participants; PFIC = progressive familial intrahepatic cholestasis; RBP = retinol-binding protein.

a Ratio (mg/g) = 1000 x alpha tocopherol (mg/dL) / total lipids (mg/dL). For alpha tocopherol concentrations reported as below the minimum quantitation limit (i.e., 0.1 mg/dL), half of the minimum quantitation limit was used as the analysis value.

b Molar Ratio (mol/mol) = 0.0734 x serum retinol (µg/dL) / serum RBP (mg/dL)

Note: Percentages are 100*n/Number of participants for each visit. The Week 72/ET time points represent the last post-baseline value obtained within 7 days of the last dose prior to the Week 72 visit.

5.2.2.1.2. Hematology

Appendix 8.1, Table 14.3.3.2 presents mean (SD), median, minimum, and maximum results of hematology parameters in the Safety Population by study visit. The changes and percent changes in assessments from baseline to each study visit are also given.

The following abnormality of the hematology profile was reported as a TEAE during the 72-weeks observation period (Appendix 8.1, Table 14.3.2.2 and Table 14.3.2.3).

- Platelet count decreased – reported in 1 participant (3.0%), of Grade 1 severity

5.2.2.1.3. Lipid Panel

Appendix 8.1, Table 14.3.3.4 summarizes the results for the lipid panel analytes (total cholesterol, LDL-C, HDL-C, and triglycerides) during the study. These lipid panel analytes were assessed as exploratory efficacy endpoints in this study; these data are presented in Appendix 8.1, Tables 14.2.11.1 (total cholesterol), 14.2.28.1 (LDL-C), 14.2.29.1 (HDL-C), and 14.2.30.1 (triglycerides).

At Week 72/ET the following changes from baseline were observed in the overall study population:

- A mean (SD) decrease in total cholesterol concentration of -2.3 (20.57) mg/dL
- A mean (SD) decrease in LDL cholesterol concentration of -8.7 (27.80) mg/dL
- A mean (SD) increase in HDL cholesterol concentration of 20.4 (68.63) mg/dL
- A mean (SD) decrease in concentration of triglycerides of -2.5 mg/dL (29.74)

5.2.2.1.4. Cholestasis Biomarkers

A summary of results of the cholestasis biomarker analysis (sBA [total, total conjugated, total and percent unconjugated], 7αC4, autotaxin, chenodeoxycholic acid, cholic acid, deoxycholic acid, FGF19, FGF21, glycochenodeoxycholic acid, glycocholic acid, glycodeoxycholic acid, glycolithocholic acid, glycoursodeoxycholic acid, lithocholic acid, taurochenodeoxycholic acid, taurocholic acid, taurodeoxycholic acid, taurolithocholic acid, tauroursodeoxycholic acid, and ursodeoxycholic acid) is provided in Appendix 8.1, Table 14.3.3.5. Serum bile acid level (change from baseline to endpoint [Week 13/ET]) was assessed as the primary efficacy endpoint. Serum bile acid levels at other time points and sBA subspecies were assessed as exploratory efficacy endpoints in this study.

5.2.2.1.5. Coagulation

A summary of clinical laboratory data for coagulation analytes is presented in Appendix 8.1, Table 14.3.3.6. International normalized ratio, aPTT, and PT were assessed as exploratory efficacy endpoints in this study.

The following results in the coagulation studies triggered a TEAE during the 72-week observation period (Appendix 8.1, Table 14.3.2.2 and Table 14.3.2.3):

- International normalized ratio increased – reported in 7 participants (21.2%), 5 of Grade 1 and 2 of Grade 2 severity
- International normalized ratio abnormal – reported in 2 participants (6.1%), both Grade 1 in severity
- Prothrombin time prolonged – reported in 1 participant (3.0%), of Grade 1 severity

5.2.2.2. Summary of Changes by Participant

A summary of the incidence of clinically-meaningful shifts from baseline for bilirubin and ALT is provided in Table 5-17. At Week 72/ET, 6/33 participants (18.2%) overall had meaningful shifts from baseline in bilirubin, including 3 participants (37.5%) with PFIC1 and 3 participants (12.0%) with PFIC2. No participant had a meaningful shift from baseline in ALT.

Table 5-17: Incidence of Clinically-Meaningful Shifts from Baseline for Bilirubin and Alanine Aminotransferase (Safety Population) during the 72-Week Observation Period

Laboratory Test Timepoint	PFIC Type PFIC1 (N=8) n/m (%)	PFIC Type PFIC2 (N=25) n/m (%)	Overall (N=33) n/m (%)
Bilirubin[a]			
Endpoint (Week 72/ET)	3/8 (37.5)	3/25 (12.0)	6/33 (18.2)
Alanine Aminotransferase[b]			
Endpoint (Week 72/ET)	0/8	0/25	0/33

Source: Appendix 8.1, Table 14.3.3.11.1

Abbreviations: ET = early termination; m = number of participants with data at each visit; n = number in a given category; N = number of participants; PFIC = progressive familial intrahepatic cholestasis; ULN = upper limit of normal.

a If baseline was ≤10 mg/dL, then a clinically-meaningful shift was an increase of ≥3 mg/dL. If baseline was >10mg/dL, then a clinically-meaningful shift was an increase of at least 5 mg/dL.

b If baseline was ≤ULN, a clinically-meaningful shift was a post-baseline level >5 × ULN. If the baseline level was >ULN, a clinically-meaningful shift was an increase of >3 × baseline and a post-baseline level >5 × ULN.

Note: Percentages are 100*n/m, where m is the number of participants with data at each visit. Baseline is the last value obtained before dosing with study drug (Day 0). The Week 72/ET time point represents the last post-baseline value obtained within 7 days of the last dose prior to the Week 72 visit.

A by-participant listing of laboratory parameter levels with significant shifts from baseline over the study is presented in Appendix 8.1, Table 14.3.3.9.

There were few notable shifts from baseline to endpoint in the fat-soluble vitamins (Table 5-18). At Week 72/ET, 7/33 participants (21.2%) overall had meaningful shifts from baseline in 25-hydroxyvitamin D, including 2/8 participants (25.0%) and 5/25 participants (20.0%) with PFIC1 and PFIC2, respectively. At Week 72/ET, 3/15 participants (20.0%) overall (all with PFIC1) had meaningful shifts from baseline in alpha tocopherol/total lipids ratio. No participant had a meaningful shift from baseline in prothrombin INR or retinol:RBP molar ratio.

Table 5-18: Incidence of Clinically-Meaningful Shifts from Baseline for Fat-soluble Vitamins (Safety Population) during the 72-Week Observation Period

Laboratory Test Timepoint	PFIC Type PFIC1 (N=8) n/m (%)	PFIC Type PFIC2 (N=25) n/m (%)	Overall (N=33) n/m (%)
25-Hydroxyvitamin D[a]			
Endpoint (Week 72/ET)	2/8 (25.0%)	5/25 (20.0%)	7/33 (21.2%)
Alpha Tocopherol/Total Lipids Ratio[b]			
Endpoint (Week 72/ET)	3/5 (60.0%)	0/10	3/15 (20.0%)
Prothrombin International Normalized Ratio[c]			
Endpoint (Week 72/ET)	0/8	0/25	0/33
Retinol:RBP Molar Ratio[d]			
Endpoint (Week 72/ET)	0/8	0/25	0/33

Source: Appendix 8.1, Table 14.3.3.14

Abbreviations: ET = early termination; m = number of participants with data at each visit; n = number in a given category; N = number of participants; PFIC = progressive familial intrahepatic cholestasis; RBP = retinol-binding protein

a A clinically-meaningful shift reflects a change from sufficient (≥20 ng/mL) at baseline to insufficient (<20 ng/mL) at the post-baseline visit.

b A clinically-meaningful shift reflects a change from sufficient (>0.8 mg/g) at baseline to insufficient (≤0.8 mg/g) at the post-baseline visit. Ratio (mg/g) = 1000 × alpha tocopherol (mg/dL) / total lipids (mg/dL); For alpha tocopherol concentrations reported as below the minimum quantitation limit (i.e., 0.1 mg/dL), half of the minimum quantitation limit was used as the analysis value.

c A clinically-meaningful shift reflects a change from sufficient (<1.2) at baseline to possibly insufficient (>1.5) at the post-baseline visit.

d A clinically-meaningful shift reflects a change from sufficient (≥0.8 mol/mol) at baseline to insufficient (<0.8 mol/mol) at the post-baseline visit. Molar Ratio (mol/mol) = 0.0734 × serum retinol (µg/dL)/serum RBP (mg/dL).

Note: Percentages are 100*n/m, where m is the number of participants with data at each visit. The Week 72/ET time point represents the last post-baseline value obtained within 7 days of the last dose prior to the Week 72 visit.

5.2.2.3. Clinically-Meaningful Laboratory Abnormalities

Serum biochemistry abnormalities triggered TEAEs within the Investigations SOC in the following clinical chemistry analytes during the 72-week observation period (Appendix 8.1, Table 14.3.2.2):

- Blood bilirubin increased – reported in 4 participants (12.1%), 1 of Grade 2 and 3 of Grade 3 severity

- Alanine aminotransferase increased – reported in 2 participants (6.1%), 1 of Grade 2 and 1 of Grade 4 severity
- Aspartate aminotransferase increased – reported in 2 participants (6.1%), 1 of Grade 2 and 1 of Grade 4 severity
- Bilirubin conjugated increased – reported in 1 participant (3.0%), of Grade 3 severity
- Blood phosphorus decreased – reported in 1 participant (3.0%), of Grade 1 severity

5.2.2.4. Hepatocellular Carcinoma Marker

Serum samples for AFP, a marker of hepatocellular carcinoma, were only drawn during the optional follow-up treatment period at every other 12-week repeating period clinic visit and at the EOT visit. A summary of AFP will be included in the planned addendum to this CSR.

5.2.3. Other Safety Evaluations

5.2.3.1. Vital Signs

Summaries of weight and height measurement z-scores are presented in Appendix 8.1, Table 14.3.4.7 and Table 14.3.4.9, respectively.

The baseline mean (SD) weight z-score was -2.7 (2.82) and -0.6 (0.88) for participants with PFIC1 and PFIC2, respectively (Appendix 8.1, Table 14.3.4.7). The mean (SD) change from baseline to Week 72/ET was 0.3 (0.92) and -0.1 (0.44) for participants with PFIC1 and PFIC2, respectively. In the overall study population, the mean (SD) change from baseline was 0.0 (0.60).

The baseline mean (SD) height z-score was -3.0 (1.47) and -1.3 (0.98) for participants with PFIC1 and PFIC2, respectively (Appendix 8.1, Table 14.3.4.9). The mean (SD) change from baseline to Week 72/ET was -0.3 (0.73) and -0.1 (0.76) for participants with PFIC1 and PFIC2, respectively. In the overall study population, the mean (SD) change from baseline was -0.2 (0.74).

5.3. Pharmacokinetics

A final analysis of the PK data will be performed after all enrolled participants have completed their final (or ET) study visit and will be included in the planned addendum to this final CSR.

5.4. Pharmacodynamics

A final analysis of the PD data will be performed after all enrolled participants have completed their final (or ET) study visit and will be included in the planned addendum to this final CSR.

5.5. Genetics

A final analysis of the Genetics data will be performed after all enrolled participants have completed their final (or ET) study visit and will be included in the planned addendum to this final CSR.

5.6. Biomarkers

A final analysis of the Biomarkers data will be performed after all enrolled participants have completed their final (or ET) study visit and will be included in the planned addendum to this final CSR.

5.7. Immunogenicity

Not applicable.

5.8. Health Economics

Not applicable.

6. OVERALL CONCLUSIONS

- Numerical reductions in sBA were observed at 13 weeks and 72 weeks of treatment with MRX in 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 reductions from baseline were observed in the ItchRO(Obs) 4-week average morning score, ItchRO(Pt) 4-week average morning score, ALT, total bilirubin, 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. At 48 weeks, 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.
- Six participants with nt-PFIC2 mutations showed a sustained multiparameter response over several time points with a normalization or ≥70% reduction in sBA, clinically-meaningful reduction or control of pruritus and a normalization of elevated transaminases and bilirubin (if elevated at baseline). These multiparameter responders also demonstrated a catch-up growth, as indicated by a positive height and weight z-score change from baseline, in contrast to non- or partial responders, who continued to on their trajectory of growth deficit with negative z-scores change from baseline.
- 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. A total of 11 participants (33.3%) experienced TEAEs of maximum severity Grade 3. A Grade 4 hyperbilirubinemia (considered potentially related to study drug) was experienced by 1 participant while a Grade 4 ALT increased and Grade 4 AST increased (both considered unlikely related to study drug) were experienced by another participant.
- 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.

- Overall, maralixibat was safe and well tolerated.

7. REFERENCES

Alissa FT, Jaffe R, Shneider BL. Update on progressive familial intrahepatic cholestasis. *J Pediatr Gastroenterol Nutr*. 2008;46(3):241-52.

Al Mehaidib A, Al Shahrani A. 1381 Progressive familial intrahepatic cholestasis in Arabs. *J Hepatol*. 2013;58:S555–S6.

Amer S, Hajira A. A comprehensive review of progressive familial intrahepatic cholestasis (PFIC): genetic disorders of hepatocanalicular transporters. *Gastroenterol Res*. 2014;7(2):39-43.

Davit-Spraul A, Gonzales E, Baussan C, Jacquemin E. Progressive familial intrahepatic cholestasis. *Orphanet J Rare Dis*. 2009;4:1.

Düll MM, Kremer AE. Treatment of pruritus secondary to liver disease. *Curr Gastroenterol Rep*. 2019;21(9):48.

EASL. EASL Clinical Practice Guidelines: management of cholestatic liver diseases. *J Hepatol*. 2009;51(2):237-67.

Gunaydin M, Bozkurter Cil AT. Progressive familial intrahepatic cholestasis: diagnosis, management, and treatment. *Hepatic Med*. 2018;10:95-104.

van Wessel D, Thompson R, Grammatikopoulos T, et al. The natural course of FIC1 deficiency and BSEP deficiency: Initial results from the NAPPED-consortium (natural course and prognosis of PFIC and effect of biliary diversion). *J Hepatol*. 2018;68:S626-S7.

van Wessel D, Thompson R, Gonzales E, et al. Genotype correlates with the natural history of severe bile salt export pump deficiency. *J Hepatol*. 2020 Feb. DOI:https://doi.org/10.1016/j.jhep.2020.02.007.