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
Chief Medical Officer:	Ed Tucker, MD, MBA 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 May 2020 (last participant last visit)
Regulatory Agency Identifier Number:	EuDRA CT No: 2013-003833-14
Final CSR Report Date:	07-May-2020
CSR Addendum Date:	13-Oct-2020

This study was performed in compliance with Good Clinical Practices and applicable regulatory requirements, including the archiving of essential documents.

SUMMARY OF CONCLUSIONS

Introduction

This CSR addendum focuses on data collected after participants' Week 72 visit, and only addresses objectives of the optional follow-up treatment period (after Week 72).

Overall Conclusions

- Improvements in pruritus previously reported at 48 weeks of treatment with MRX, continued throughout the study. Numerical improvement was observed in participants with PFIC2 and PFIC1 in ItchRO(Obs) weekly morning average, weekly average, and weekly evening average scores. Improvements were greater in participants with PFIC2 than those with PFIC1, and generally, participants with nt-PFIC2 showed a better response than those with t-PFIC2.
- Previously reported numerical reductions in sBA observed at 13 weeks and 72 weeks of treatment with MRX in participants with PFIC2 continued throughout the study. These improvements in sBA levels were not evident in participants with PFIC1.
- The numerical improvement in ALT described for participants with PFIC2 in the LUM001-501 Final CSR continued throughout the study. A numerical improvement in AST was also observed. These improvements were not observed in participants with PFIC1.
- Previously reported numerical increases of treatment in total bilirubin, and direct bilirubin, in participants with PFIC2 and PFIC1 from baseline to Week 72 were not sustained long term; by Week 204 total bilirubin levels had returned to close to baseline (participants with nt-PFIC2) or showed a reduction (improvement) (participants with PFIC1), and by Week 204 direct bilirubin levels showed a reduction (improvement) from baseline (participants with nt-PFIC2 and PFIC1).
- The change from baseline in height, weight, and BMI z-scores was not statistically significant regardless of analysis visit, in participants with PFIC1, PFIC2, or in the overall study population, with the exception of the BMI z-scores at 2 analysis visits (for participants with PFIC2 at Week 2 and Week 252, and participants with PFIC1 at Week 252).
- In post hoc analyses, 7/19 participants with nt-PFIC2 experienced control of the sBA levels to below 102 µmol/L or a 75% reduction from baseline resulting in clinically meaningful reductions in pruritus ($\geq$1.0 reduction in ItchRO(Obs) or score below 1.0), normalization of bilirubin, ALT, and AST if elevated, and improvement in height z-score. These responses happened at both 280 µg/kg once daily and 280 µg/kg twice daily dosing of MRX. All 7 of these participants demonstrating this response to maralixibat treatment remained on the study for over 5 years.
- Serious AEs were experienced by 15 participants (45.5%) during the study. The only SAEs reported for more than 1 participant were abdominal pain, diarrhea, and gastroenteritis, 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. No SAEs were experienced by participants on a dose of MRX of 280 µg/kg BID.

- Overall, reported TEAEs were generally mild or moderate in severity.
- Fourteen participants (42.4%) experienced CTCAE Grade 3 or CTCAE Grade 4 TEAEs during the study. A total of 12 participants (36.4%) experienced TEAEs of maximum severity Grade 3. A Grade 4 event of hyperbilirubinemia (considered potentially related to study drug) was experienced by 1 participant while Grade 4 events of ALT increased and 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 26 participants (78.8%) overall.
- The most common TEAEs reported included the following: pyrexia (20 participants [60.6%]), diarrhea (19 participants [57.6%]), cough (18 participants [54.5%]), and vomiting (17 participants [51.5%]).
- A total of 10 participants (30.3%) experienced TEAEs that led to permanent treatment discontinuation. Treatment-emergent AEs leading to permanent treatment discontinuation in more than 1 participant were reported as blood bilirubin increased and disease progression.
- No deaths were reported in the study.
- Long-term safety data presented here were consistent with those reported in the LUM001-501 Final CSR, during the first 72 weeks of treatment with MRX.
- Overall, MRX was safe and well tolerated.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	DEFINITION/EXPLANATION
AE	adverse event
AFP	alpha-fetoprotein
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASBTi	apical sodium-dependent bile acid transporter inhibitor
AST	aspartate aminotransferase
BID	twice daily
BMI	body mass index
BSEP	bile salt export pump
C4	7α hydroxyl-4-cholesten-3-one; an indirect method of bile acid synthesis
CFB	change from baseline
CI	confidence interval
CSR	clinical study report
CSS	Clinician Scratch Score
CTCAE	Common Terminology Criteria for Adverse Events
EOT	end-of-treatment
ET	early termination
fBA	fecal bile acid
FGF	Fibroblast growth factor
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
HDL-C	high-density lipoprotein cholesterol
INR	International normalized ratio
ItchRO™	Itch Reported Outcome
ItchRO(Obs)™	Itch Reported Outcome (Observer)
ItchRO(Pt)™	Itch Reported Outcome (Patient)
LDL-C	low-density lipoprotein cholesterol
MedDRA	Medical Dictionary for Regulatory Activities
MRX	maralixibat chloride
nt-PFIC2	non-truncating PFIC2 mutation
PFIC	progressive familial intrahepatic cholestasis
PT	preferred term
QD	once daily
RBP	retinol-binding protein
SAE	serious adverse event
SAP	statistical analysis plan

ABBREVIATION	DEFINITION/EXPLANATION
sBA	serum bile acid
SD	standard deviation
SOC	system organ class (MedDRA)
t-PFIC2	truncating PFIC2 mutation
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

1. INTRODUCTION

This CSR addendum focuses on data collected after participants' Week 72 visit, and only addresses objectives of the optional follow-up treatment period (after Week 72), as presented in Protocol LUM001-501, v4.1, 08 February 2019. These objectives and their endpoints are presented in Section 2. The efficacy endpoints presented in this CSR addendum are exploratory endpoints.

Study objectives up to and including Week 72, and the primary and secondary endpoints were fully addressed in the LUM001-501 Final CSR, v1.0, 07 May 2020.

Overall conclusions reached in the LUM001-501 Final CSR were as follows:

- 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 CFB 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 CFB to Week 72/ET. Updated results after Week 72 are presented in Section 5.1.3.3.
- At 13 weeks of treatment, numerical reductions from baseline were observed in the ItchRO(Obs) 4-week morning average score, ItchRO(Pt) 4-week morning average score, ALT, total bilirubin, and direct bilirubin, in participants with PFIC2 and PFIC1. Updated results after Week 72 are presented in Section 5.1.3.3 (ALT, total and direct bilirubin) and Section 5.1.3.1 (ItchRO[Obs]).
- Participants with PFIC2 continued to show numerical improvement in sBA and ALT at 72 weeks of treatment, and in ItchRO(Obs) 4-week morning average score and ItchRO(Pt) 4-week morning average score at 48 weeks of treatment. At 48 weeks, participants with PFIC1 continued to show numerical improvement in the ItchRO(Obs) 4-week morning average score and ItchRO(Pt) 4-week morning average score. Updated results after Week 72 are presented in Section 5.1.3.3 (sBA and ALT) and Section 5.1.3.1 (ItchRO[Obs] and ItchRO[Pt]).
- 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 CFB, in contrast to non- or partial responders, who continued to on their trajectory of growth deficit with negative z-scores CFB. Updated results on participants that showed a sustained multiparameter response over time are presented in Section 5.1.4.
- 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. Updated SAE results using all available data are presented in Section 5.2.1.4.

- Overall, reported TEAEs were generally mild or moderate in severity. Updated TEAE results using all available data are presented in Section 5.2.1.2.
- A total of 11 participants (33.3%) had TEAEs of maximum severity Grade 3, and 2 (6.1%) participants had TEAEs of maximum severity of Grade 4. A Grade 4 event of hyperbilirubinemia (considered potentially related to study drug) was experienced by 1 participant while a Grade 4 event of ALT increased and Grade 4 event of 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%]). The most frequently reported treatment-related TEAEs included diarrhea (10 participants [30.3%]); abdominal pain (7 participants [21.2%]); abdominal pain upper (6 participants [18.2%]), vomiting (5 participants [15.2%]), and INR increased (5 participants [(15.2%]).
- A total of 5 participants (15.2%) experienced TEAEs that led to permanent treatment discontinuation. 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. Updated TEAE results leading to discontinuation using all available data are presented in Section 5.2.1.5.
- No deaths were reported in the study.
- Overall, MRX was safe and well tolerated.

2. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Optional Follow-up Treatment Period (After Week 72)	
• To offer eligible participants in the LUM001-501 study continued study treatment beyond Week 72 until the first of the following occurs: (i) the participants are eligible to enter another MRX study or (ii) MRX is available commercially	• NA
• To obtain safety and efficacy data in participants treated long term on MRX	Safety Endpoints: • Incidence of TEAEs including SAEs, related to study drug, leading to withdrawal, special interest TEAEs, along with TEAEs by severity • CFB in clinical safety laboratory values at each analysis visit (where applicable) • Observed serum AFP values at each analysis visit (where applicable) • Physical examination findings, including body height, weight, and BMI at each analysis visit • Vital signs at each analysis visit • Concomitant medication usage • Study drug exposure, including weekly average dose, total drug exposure, and treatment duration • Plasma sample MRX concentrations at each analysis visit (where applicable) Exploratory Efficacy Endpoints: • CFB in pruritus as measured by ItchRO(Obs) weekly average score and weekly morning average score at Weeks 4, 8, 28, 48, 48/LOCF, 86, 98, 110, 122, 122/LOCF, and every 12 weeks (where applicable) through the end of treatment • CFB in pruritus as measured by ItchRO(Obs) weekly evening average score at Weeks 4, 8, 13, 28, 48, 48/LOCF, 86, 98, 110, 122, 122/LOCF, and every 12 weeks (where applicable) through the end of treatment • CFB in pruritus as measured by ItchRO(Pt) weekly average score, weekly morning average score, and weekly evening average score at Weeks 4, 8, 13, 28, 48, 48/LOCF, 86, 98, 110, 122, 122/LOCF, and every 12 weeks (where applicable) through the end of treatment • Responder analysis: pruritus response rates as measured by ItchRO (Obs and Pt) weekly morning average scores at Weeks 13, 48, 48/LOCF, 98, 122, 122/LOCF, and every 12 weeks (where applicable) through the end of treatment; Responder definitions include CFB of ≤-1.0, ≤-1.33, ≤-1.5, and ≤1.75 • CFB in the CSS score at Weeks 2, 4, 8, 13, 24, 36, 48, 60, 72, 72/LOCF, 84, 96, 108, 120, 124/LOCF, and every 12 weeks (where applicable) through the end of treatment

	• CFB in fasting sBA level at Weeks 4, 8, 24, 36, 48, 60, 72, 72/LOCF, 84, 96, 108, 120, 124/LOCF, and every 12 weeks (where applicable) through the end of treatment • CFB in ALT, AST, and bilirubin (total and direct) levels at Weeks 4, 8, 24, 36, 48, 60, 72, 72/LOCF, 84, 96, 108, 120, 124/LOCF, and every 12 weeks (where applicable) through the end of treatment • CFB for ALP, C4, total cholesterol, LDL-C, and GGT at Weeks 4, 8, 13, 24, 36, 48, 60, 72, 72/LOCF, 84, 96, 108, 120, 124/LOCF, and every 12 weeks (where applicable) through the end of treatment • Responder analysis: sBA response rates at Weeks 13, 48, 72, 72/LOCF, 96, 120, 124/LOCF, and every 12 weeks (where applicable) through the end of treatment. Responder definitions include % CFB of ≤-75, sBA ≤102 µmol/L, % CFB of ≤-75 or sBA ≤102 µmol/L, and sBA ≤8.5 µmol/L (normalization) • Responder analysis: sBA and ItchRO(Obs) weekly morning average scores at Weeks 13, 48, 72 (sBA only), 96 (Week 98 for ItchRO data), 120 (Week 122 for ItchRO data), 124/LOCF (Week 122/LOCF for ItchRO data), and every 12 weeks (where applicable) through the end of treatment. Responder definitions include each of the sBA responder definitions combined with an ItchRO(Obs) weekly morning average CFB score of ≤-1.0 point • Responder analysis: liver function lab tests (C4, AST, ALT, and total bilirubin) at Weeks 13, 48, 72, 72/LOCF, 96, 120, 124/LOCF, and every 12 weeks (where applicable) through the end of treatment. Responder definitions include C4 % CFB ≥100, shift from >ULN at baseline to normal in AST, shift from >ULN at baseline to normal in ALT, and shift from >ULN at baseline to normal in total bilirubin • CFB for PedsQL Total Scale Score (parent), Multidimensional Fatigue Scale Score (parent) and Family Impact total Scale Score at Weeks 13, 13/ET, 24, 48, 72, 72/LOCF, 84, 96, 108, 120, 124, 124/LOCF, and every 12 weeks (where applicable) through the end of treatment • CFB in height, weight, and BMI z-scores at Weeks 2, 4, 8, 13, 24, 36, 48, 60, 72, 72/LOCF, 84, 96, 108, 120, 124/LOCF, and every 12 week (where applicable) through the end of treatment <u>Exploratory Efficacy Variables Presented Only as Participant Listings</u>: • Patient impression of change • Caregiver impression of change • Caregiver global therapeutic benefit • Autotaxin • Activated partial thromboplastin time • Prothrombin time • International normalized ratio • Triglycerides • High-density lipoprotein cholesterol • Fibroblast growth factor -19 • Fibroblast growth factor -21

	• sBA sub-species (taurocholic acid, taurochenodeoxycholic acid, tauroursodeoxycholic acid, taurodeoxycholic acid, taurolithocholic acid, glycocholic acid, glycoursodeoxycholic acid, glycochenodeoxycholic acid, glycodeoxycholic acid, glycolithocholic acid, cholic acid, ursodeoxycholic acid, chenodeoxycholic acid, deoxycholic acid, and lithocholic acid) and the ratio of cholic acid and chenodeoxycholic acid
• To explore a twice a day (BID) dosing regimen and higher daily dosing of MRX.	• Incidence of TEAEs including SAEs, related to study drug, leading to withdrawal, special interest TEAEs, along with TEAEs by severity
• To identify genetic indicators of treatment response, including use of exome sequencing	• Presentation of genotype data in a listing
• To assess the level of AFP, a marker of hepatocellular carcinoma	• Observed serum AFP values at each analysis visit
• To assess palatability of the MRX formulation	• Assessment of the palatability of the MRX formulation by-proxy in participants <4 years old and by participant questionnaire in children ≥4 years old
Exploratory Objective	
• To allow the possibility of analysis of serum markers of treatment response using metabolomic and proteomic analysis on previously collected serum samples	• This was outside the scope of this CSR addendum; metabolomic and proteomic analysis was not included in the final analyses.

Abbreviations: AE = adverse event; AFP = alpha-fetoprotein; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; C4 = 7α hydroxyl-4-cholesten-3-one; CSS = Clinician Scratch Scale; EOT = end of treatment; ET = early termination; GGT = gamma-glutamyl transpeptidase; ItchRO(Obs) = Itch Reported Outcome (Observer); ItchRO(Pt) = Itch Reported Outcome (Patient); LDL-C = low-density lipoprotein cholesterol; LOCF = last observation carried forward; MRX = maralixibat; NA = not applicable; PedsQL = Pediatric Quality of Life Inventory; SAEs = serious adverse events; sBA = serum bile acid; TEAE = treatment-emergent adverse event

3. INVESTIGATIONAL PLAN

The study design, investigators and study administrative structure, study population, study assessments and procedures, and data quality assurance remain unchanged from those presented in detail in the LUM001-501 Final CSR, v1.0, 07 May 2020, with additional details available in the Protocol LUM001-501, v4.1, 08 February 2019. This CSR addendum is based on final data, after all enrolled participants under the parameters of Protocol Amendment 4, dated 20 December 2016, had completed their final (or ET) study visit.

3.1. Standardization of Laboratory Procedures

Documentation of interlaboratory standardization methods and laboratory quality assurance procedures for all laboratories used during the study that were not included in the LUM001-501 Final CSR is provided in Appendix 9.10.

3.2. Clinical Quality Assurance Audits

Certificates for all audits conducted during the study that were not included in the LUM001-501 Final CSR can be found in Appendix 9.8.

3.3. Statistical Analysis

3.3.1. Statistical Analysis Plan

This CSR addendum reports the final analyses, which was the fourth and final planned analysis. The planned analyses, comparisons, statistical tests, and determination of sample size are described in the final version of the SAP Amendment 3 (Appendix 9.9). The tables, figures, and listings presented in Appendix 8.1 and Appendices 8.2.1 through 8.2.9 of this CSR include all data collected throughout the study.

3.3.2. 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 Amendment 3 (Appendix 9.9). Notable changes, as implemented by Amendment 3 of the SAP include the following:

- An ITT analysis population was added for the final analysis. Each sibling pair was included in the ITT analysis population. The ITT population was used as the analysis set for all final efficacy analyses.
- Visit-based assessments have been mapped to analysis visits based on study day, where study day was derived relative to the date of first dose of study drug.
- Visit-based analyses were performed by analysis visit, rather than clinic visit. Analyses of all efficacy variables, regardless of drug interruptions, were performed using the analysis visits. For participants with an extended drug interruption, efficacy assessments after the interruption were essentially treated as if the participant was on study drug during the period of time that the participant was off study drug. The analysis visit windows were also used for all visit-based safety assessments that occurred before an extended

(>28-day) drug interruption (due to a protocol amendment), including those participants without such a drug interruption.

- For each primary and secondary efficacy variable (except ItchRO(Obs) 4-week morning average score), and select exploratory variables, an analysis by PFIC2 subtype (truncating PFIC2, non-truncating PFIC2) was added.
- LOCF records at Week 72 and Week 124 (Week 48 and Week 122 for ItchRO variables) were added for visit-based assessments. Applicable efficacy and safety endpoints were updated to reflect this change.
- ItchRO 2-week morning and evening average scores were replaced with weekly morning and evening average scores.
- Pruritus response rates as measured by ItchRO(Obs) and ItchRO(Pt) weekly morning average scores were added.
- Efficacy analysis by MRX dose has been removed, as it is no longer believed to be relevant.
- Efficacy analysis by PFIC2 subtypes (non-truncated and truncated) have been added for select efficacy variables.
- z-scores for body height, body weight, and BMI were considered as exploratory efficacy endpoints rather than safety.
- AESI groups were changed for consistency with other MRX Phase 2 analysis plans.
- A separate analysis presentation for treatment compliance during BID dosing was removed.

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

Amendment 3 of the SAP was finalized and approved after database lock; however, analysis decisions were not changed after database lock. No datasets were given to the biostatistician until the SAP was final. It should be noted that this was an open-label study.

4. STUDY PARTICIPANTS

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

4.1. Disposition of Participants

A summary of participant disposition is presented in Table 4-1, by PFIC subtype, and by PFIC2 phenotype: non-truncating (mild to moderate phenotype with residual BSEP [liver-specific transporter] function) or truncating (severe phenotype without residual BSEP function or complete absence of BSEP).

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. Four participants (12.1%) were dose reduced during the study.

A total of 22 participants (66.7%) remained in the study at Week 72, with a total of 15 participants (45.5%) completing study treatment through Week 124. Three participants (9.1%) discontinued between Week 72 and Week 124; 2 participants (6.1%) due to an AE; 1 participant due to other reason.

A total of 12 participants (36.4%) completed study treatment through EOT. Three participants (9.1%) discontinued between Week 124 and EOT; 1 participant (3.0%) each due to an AE, progressive disease, and other reason.

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

		PFIC2			
Status or Variable	**PFIC1**	**nt-PFIC2**	**t-PFIC2**	**Overall**	**Overall**
Screened for eligibility	8	19	6	25	37
Screen failure under original protocol[a]					4
Screen failure under protocol amendment					1
Enrolled	8	19	6	25	33
Number of families with siblings enrolled in the study	0	1	1	2	2
Total number of siblings[b]	0	2	2	4	4
Safety Population[c]	8	19	6	25	33
ITT Population n (%)[c]	8 (100.0)	19 (100.0)	6 (100.0)	25 (100.0)	33 (100.0)
Down-titrated during study n (%)	1 (12.5)	3 (15.8)	0	3 (12.0)	4 (12.1)
Consented to PA3 and completed at least 1 post-Week 72 assessment	5 (62.5)	9 (47.4)	3 (50.0)	12 (48.0)	17 (51.5)
Consented to PA4 and completed at least 1 post-Week 124 assessment	5 (62.5)	9 (47.4)	1 (16.7)	10 (40.0)	15 (45.5)

Status or Variable	PFIC1	PFIC2			Overall
		nt-PFIC2	t-PFIC2	Overall	
Completed study treatment through Week 72 n (%)	6 (75.0)	13 (68.4)	3 (50.0)	16 (64.0)	22 (66.7)
Discontinued prior to Week 72 n (%)	2 (25.0)	6 (31.6)	3 (50.0)	9 (36.0)	11 (33.3)
Reason for discontinuation prior to Week 72 n (%)					
Adverse event	0	2 (10.5)	1 (16.7)	3 (12.0)	3 (9.1)
Death	0	0	0	0	0
Lost to follow-up	0	0	0	0	0
Non-compliance with study drug	0	1 (5.3)	0	1 (4.0)	1 (3.0)
Physician decision	1 (12.5)	0	0	0	1 (3.0)
Pregnancy	0	0	0	0	0
Progressive disease	0	0	2 (33.3)	2 (8.0)	2 (6.1)
Protocol violation	0	0	0	0	0
Study terminated by sponsor	0	0	0	0	0
Withdrawal by caregiver	1 (12.5)	1 (5.3)	0	1 (4.0)	2 (6.1)
Withdrawal by participant	0	1 (5.3)	0	1 (4.0)	1 (3.0)
Other[d]	0	1 (5.3)	0	1 (4.0)	1 (3.0)
Completed study treatment through Week 124 n (%)	5 (62.5)	9 (47.4)	1 (16.7)	10 (40.0)	15 (45.5)
Discontinued between Week 72 and Week 124 n (%)	0	1 (5.3)	2 (33.3)	3 (12.0)	3 (9.1)
Reason for discontinuation between Week 72 and Week 124 n (%)					
Adverse event	0	0	2 (33.3)	2 (8.0)	2 (6.1)
Death	0	0	0	0	0
Lost to follow-up	0	0	0	0	0
Non-compliance with study drug	0	0	0	0	0
Physician decision	0	0	0	0	0
Pregnancy	0	0	0	0	0
Progressive disease	0	0	0	0	0
Protocol violation	0	0	0	0	0
Study terminated by sponsor	0	0	0	0	0
Withdrawal by caregiver	0	0	0	0	0
Withdrawal by participant	0	0	0	0	0
Other[e]	0	1 (5.3)	0	1 (4.0)	1 (3.0)

Status or Variable	PFIC1	PFIC2			Overall
		nt-PFIC2	t-PFIC2	Overall	
Completed study treatment through EOT n (%)	4 (50.0)	8 (42.1)	0	8 (32.0)	12 (36.4)
Discontinued between Week 124 and EOT n (%)	1 (12.5)	1 (5.3)	1 (16.7)	2 (8.0)	3 (9.1)
Reason for discontinuation between Week 124 and EOT n (%)					
Adverse event	1 (12.5)	0	0	0	1 (3.0)
Death	0	0	0	0	0
Lost to follow-up	0	0	0	0	0
Non-compliance with study drug	0	0	0	0	0
Physician decision	0	0	0	0	0
Pregnancy	0	0	0	0	0
Progressive disease	0	0	1 (16.7)	1 (4.0)	1 (3.0)
Protocol violation	0	0	0	0	0
Study terminated by sponsor	0	0	0	0	0
Withdrawal by caregiver	0	0	0	0	0
Withdrawal by participant	0	0	0	0	0
Other[e]	0	1 (5.3)	0	1 (4.0)	1 (3.0)

Source: Appendix 8.1, Table 14.1.1
Abbreviations: EOT = end of treatment; ITT = intent-to-treat; n = number in a given category; nt-PFIC2 = non-truncating PFIC2; PFIC = progressive familial intrahepatic cholestasis; t-PFIC2 = truncating PFIC2
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 and ITT analysis populations.
c The Safety and ITT populations included all participants assigned to study treatment who received any amount of study drug. The ITT population was used for efficacy analyses.
d 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 16.2.2.2).
e Participant 003053 had a liver transplantation on Study Day 1589, and Participant 027052 had a liver transplantation on Study Day 564.
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:

- Informed consent form 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

Major protocol deviations are found in Appendix 8.2, Listing 16.3.2. Three participants during the study were identified as having a major protocol deviation: 2 violations of inclusion/exclusion criteria and 1 deviation from LUM001-501 study protocol procedures. The violations of inclusion/exclusion criteria were identified for 2 participants who were enrolled on historical sBA values rather than results from Screening. The deviation from LUM001-501 study protocol procedures was identified in 1 participant who stopped taking study drug but did not inform the study site. The participant was considered an early termination from the study and completed the early termination/Week 72 visit.

4.3. Populations Analyzed

Table 4-1 shows the number of participants in the Safety Population and the ITT Population. A total of 33 participants (8 with PFIC1, 19 with nt-PFIC2, and 6 with t-PFIC2) were included in the Safety Population and the ITT Population, which included all participants who were assigned to study treatment and received at least 1 dose of study drug.

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 (SE) overall age was 4.2 years (0.56), 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 1 race.

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

Variable Statistic or Category	PFIC1 (N=8)	PFIC2 nt-PFIC2 (N=19)	PFIC2 t-PFIC2 (N=6)	PFIC2 Overall (N=25)	Overall (N=33)
Age (years)[a]					
n	8	19	6	25	33
Mean (SE)	3.0 (0.71)	4.1 (0.79)	6.3 (1.38)	4.6 (0.70)	4.2 (0.56)
Median	2.0	3.0	7.0	4.0	3.0
Min, Max	1, 7	1, 13	1, 10	1, 13	1, 13

Variable Statistic or Category	PFIC1 (N=8)	PFIC2 nt-PFIC2 (N=19)	PFIC2 t-PFIC2 (N=6)	PFIC2 Overall (N=25)	Overall (N=33)
Age category[a] n (%)					
<2 years	1 (12.5)	5 (26.3)	1 (16.7)	6 (24.0)	7 (21.2)
2 to 4 years	5 (62.5)	9 (47.4)	1 (16.7)	10 (40.0)	15 (45.5)
5 to 8 years	2 (25.0)	2 (10.5)	2 (33.3)	4 (16.0)	6 (18.2)
9 to 12 years	0	2 (10.5)	2 (33.3)	4 (16.0)	4 (12.1)
13 to 18 years	0	1 (5.3)	0	1 (4.0)	1 (3.0)
Gender n (%)					
Male	6 (75.0)	6 (31.6)	2 (33.3)	8 (32.0)	14 (42.4)
Female	2 (25.0)	13 (68.4)	4 (66.7)	17 (68.0)	19 (57.6)
Height z-score					
n	8	19	6	25	33
Mean (SE)	-2.963 (0.5194)	-1.066 (0.2296)	-1.982 (0.2144)	-1.286 (0.1968)	-1.693 (0.2290)
Median	-2.500	-1.356	-1.901	-1.493	-1.653
Min, Max	-6.06, -1.62	-2.73, 0.77	-2.81, -1.34	-2.81, 0.77	-6.06, 0.77
Weight z-score					
n	8	19	6	25	33
Mean (SE)	-2.704 (0.9963)	-0.402 (0.1764)	-1.331 (0.3607)	-0.625 (0.1755)	-1.129 (0.3081)
Median	-1.775	-0.216	-1.267	-0.342	-0.844
Min, Max	-9.14, -0.29	-1.83, 0.60	-2.73, -0.20	-2.73, 0.60	-9.14, 0.60
BMI z-score					
n	8	19	6	25	33
Mean (SE)	-0.035 (0.4645)	0.463 (0.2160)	-0.036 (0.3118)	0.344 (0.1826)	0.252 (0.1767)
Median	-0.279	0.372	0.078	0.165	0.049
Min, Max	-2.39, 2.01	-1.12, 1.94	-1.13, 0.88	-1.13, 1.94	-2.39, 2.01

Variable Statistic or Category	PFIC1 (N=8)	PFIC2 nt-PFIC2 (N=19)	PFIC2 t-PFIC2 (N=6)	PFIC2 Overall (N=25)	Overall (N=33)
Race n (%)					
American Indian or Alaska Native	0	0	0	0	0
Asian	2 (25.0)	0	1 (16.7)	1 (4.0)	3 (9.1)
Black or African American	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
White	6 (75.0)	18 (94.7)	2 (33.3)	20 (80.0)	26 (78.8)
More than 1 race	0	1 (5.3)	0	1 (4.0)	1 (3.0)
Not reported	0	0	3 (50.0)	3 (12.0)	3 (9.1)
Ethnicity n (%)					
Hispanic or Latino	0	1 (5.3)	0	1 (4.0)	1 (3.0)
Not Hispanic or Latino	8 (100.0)	18 (94.7)	3 (50.0)	21 (84.0)	29 (87.9)
Not Reported	0	0	3 (50.0)	3 (12.0)	3 (9.1)
Country n (%)					
France	0	0	3 (50.0)	3 (12.0)	3 (9.1)
Great Britain	3 (37.5)	9 (47.4)	2 (33.3)	11 (44.0)	14 (42.4)
Poland	0	1 (5.3)	0	1 (4.0)	1 (3.0)
United States	5 (62.5)	9 (47.4)	1 (16.7)	10 (40.0)	15 (45.5)

Source: Appendix 8.1, Table 14.1.3
Abbreviations: BMI = body mass index; Max = maximum; Min = minimum; n = number in a given category; N = number of participants; nt-PFIC2 = non-truncating PFIC2; PFIC = progressive familial intrahepatic cholestasis; SE = standard error of the mean; t-PFIC2 = truncating PFIC2
a Age at time of baseline visit.
Note: Percentages are 100*n/N

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 32.23 months, with a range of 4.6-127.0 months. 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, with oral therapies most frequently reported (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, 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	PFIC1 (N=8)	PFIC2 nt-PFIC2 (N=19)	PFIC2 t-PFIC2 (N=6)	PFIC2 Overall (N=25)	Overall (N=33)
Time Since Original Diagnosis of PFIC (months)					
n	8	19	6	25	33
Median (minimum, maximum)	23.38 (12.5, 78.9)	27.14 (4.6, 118.6)	54.88 (18.5, 127.0)	33.08 (4.6, 127.0)	32.23 (4.6, 127.0)
Family History of PFIC n (%)					
Yes	3 (37.5)	3 (15.8)	0	3 (12.0)	6 (18.2)
No	5 (62.5)	15 (78.9)	3 (50.0)	18 (72.0)	23 (69.7)
Unknown	0	1 (5.3)	3 (50.0)	4 (16.0)	4 (12.1)
Used Anything to Treat Itch in the Past n (%)					
Yes	7 (87.5)	16 (84.2)	5 (83.3)	21 (84.0)	28 (84.8)
No	1 (12.5)	3 (15.8)	1 (16.7)	4 (16.0)	5 (15.2)
Type of Therapy Used to Treat Itch in the Past[a] n (%)					
Topical	1 (12.5)	3 (15.8)	1 (16.7)	4 (16.0)	5 (15.2)
Oral	7 (87.5)	15 (78.9)	5 (83.3)	20 (80.0)	27 (81.8)
Other	2 (25.0)	9 (47.4)	0	9 (36.0)	11 (33.3)
Specific Therapy Used to Treat Itch in the Past n (%)					
Topical Antihistamines	1 (12.5)	2 (10.5)	0	2 (8.0)	3 (9.1)
Topical Calcineurin Inhibitors	0	1 (5.3)	0	1 (4.0)	1 (3.0)
Topical Corticosteroids	0	2 (10.5)	1 (16.7)	3 (12.0)	3 (9.1)
Topical Local Anesthetics	1 (12.5)	1 (5.3)	0	1 (4.0)	2 (6.1)
Topical Menthol	0	1 (5.3)	0	1 (4.0)	1 (3.0)
Oral Anticonvulsants	1 (12.5)	4 (21.1)	1 (16.7)	5 (20.0)	6 (18.2)
Oral Antidepressants	0	0	2 (33.3)	2 (8.0)	2 (6.1)
Oral Antihistamines	3 (37.5)	11 (57.9)	1 (16.7)	12 (48.0)	15 (45.5)
Oral Anti-oxidants	0	1 (5.3)	0	1 (4.0)	1 (3.0)
Oral Binding Resins	2 (25.0)	9 (47.4)	1 (16.7)	10 (40.0)	12 (36.4)
Oral Enzyme Inducers	5 (62.5)	12 (63.2)	5 (83.3)	17 (68.0)	22 (66.7)

Variable Statistic or Category	PFIC1 (N=8)	PFIC2 nt-PFIC2 (N=19)	PFIC2 t-PFIC2 (N=6)	PFIC2 Overall (N=25)	Overall (N=33)
Oral Opiate Antagonists	2 (25.0)	5 (26.3)	1 (16.7)	6 (24.0)	8 (24.2)
Oral Serotonin Antagonists	2 (25.0)	5 (26.3)	0	5 (20.0)	7 (21.2)
Oral Ursodiol	5 (62.5)	14 (73.7)	3 (50.0)	17 (68.0)	22 (66.7)
Other Hemofiltration (MARS)	0	1 (5.3)	0	1 (4.0)	1 (3.0)
Other Nasal Biliary Drainage	0	1 (5.3)	0	1 (4.0)	1 (3.0)
Other	2 (25.0)	7 (36.8)	0	7 (28.0)	9 (27.3)

Source: Appendix 8.1, Table 14.1.4
Abbreviations: MARS = molecular adsorbent recirculating system; n = number in a given category; N = number of participants; nt-PFIC2 = non-truncating PFIC2; PFIC = progressive familial intrahepatic cholestasis; SE = standard error of the mean; t-PFIC2 = truncating PFIC2
a Each medication/therapy was pre-specified on the case report form; see Appendix 8.1, Table 14.1.5 for complete list.
Note: Percentages are 100*n/N.

A summary of CSS scores and ItchRO weekly average (both observer and patient), and ItchRO weekly morning average and weekly evening average (observer only) 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 (SE) scores were 2.274 (0.1439), 2.295 (0.1439), and 2.256 (0.1522) for the weekly average score, weekly morning average score, and weekly evening average score, respectively. The baseline ItchRO(Pt) mean (SE) scores was 2.201 (0.2753) for the weekly average score.

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

Variable Statistic or Category	PFIC1 (N=8)	PFIC2 nt-PFIC2 (N=19)	PFIC2 t-PFIC2 (N=6)	PFIC2 Overall (N=25)	Overall (N=33)
Clinician Scratch Scale Score[a]					
n	8	19	6	25	33
Mean (SE)	2.8 (0.16)	2.9 (0.24)	2.7 (0.21)	2.9 (0.19)	2.8 (0.15)
Median	3.0	3.0	3.0	3.0	3.0
Min, Max	2, 3	0, 4	2, 3	0, 4	0, 4
0 n (%)	0	1 (5.3)	0	1 (4.0)	1 (3.0)
1 n (%)	0	1 (5.3)	0	1 (4.0)	1 (3.0)
2 n (%)	2 (25.0)	1 (5.3)	2 (33.3)	3 (12.0)	5 (15.2)
3 n (%)	6 (75.0)	11 (57.9)	4 (66.7)	15 (60.0)	21 (63.6)
4 n (%)	0	5 (26.3)	0	5 (20.0)	5 (15.2)

Variable Statistic or Category	PFIC1 (N=8)	PFIC2 nt-PFIC2 (N=19)	PFIC2 t-PFIC2 (N=6)	PFIC2 Overall (N=25)	Overall (N=33)
ItchRO(Obs) Weekly Average Score[b]					
n	8	19	6	25	33
Mean (SE)	2.138 (0.2637)	2.139 (0.1945)	2.881 (0.2777)	2.317 (0.1721)	2.274 (0.1439)
Median	2.071	1.929	2.714	2.286	2.214
Min, Max	1.07, 3.43	0.14, 3.29	2.21, 3.79	0.14, 3.79	0.14, 3.79
ItchRO(Pt) Weekly Average Score[b]					
n	2	5	4	9	11
Mean (SE)	1.393 (0.2500)	2.086 (0.4537)	2.750 (0.3554)	2.381 (0.3030)	2.201 (0.2753)
Median	1.393	2.357	2.607	2.357	2.214
Min, Max	1.14, 1.64	0.43, 3.14	2.14, 3.64	0.43, 3.64	0.43, 3.64
ItchRO(Obs) Weekly Morning Average Score[c]					
n	8	19	6	25	33
Mean (SE)	2.307 (0.3045)	2.090 (0.1890)	2.929 (0.2045)	2.291 (0.1667)	2.295 (0.1439)
Median	2.000	2.143	2.857	2.286	2.286
Min, Max	1.14, 3.60	0.14, 3.14	2.29, 3.57	0.14, 3.57	0.14, 3.60
ItchRO(Obs) Weekly Evening Average Score[c]					
n	8	19	6	25	33
Mean (SE)	1.985 (0.2626)	2.188 (0.2032)	2.833 (0.3565)	2.343 (0.1818)	2.256 (0.1522)
Median	2.071	2.000	2.571	2.143	2.143
Min, Max	1.00, 3.43	0.14, 3.43	2.00, 4.00	0.14, 4.00	0.14, 4.00

Source: Appendix 8.1, Table 14.1.4

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; nt-PFIC2 = non-truncating PFIC2; PFIC = progressive familial intrahepatic cholestasis; SE = standard error of the mean; t-PFIC2 = truncating PFIC2

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 Weekly Morning/Evening Average Score = sum of morning/evening scores divided by the number of days ItchRO was completed, based upon up to 7 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	PFIC1 (N=8)	PFIC2			Overall (N=33)
		nt-PFIC2 (N=19)	t-PFIC2 (N=6)	Overall (N=25)	
Serum Bile Acid (µmol/L)					
n	8	19	6	25	33
Mean (SE)	261.81 (35.205)	373.35 (37.154)	404.92 (45.886)	380.93 (29.995)	352.05 (25.658)
Median	216.40	422.88	389.56	407.63	373.89
Min, Max	159.7, 423.4	34.3, 601.4	255.7, 602.1	34.3, 602.1	34.3, 602.1
Alkaline Phosphatase (U/L)					
n	8	19	6	25	33
Mean (SE)	696.6 (77.78)	467.2 (35.88)	464.8 (58.21)	466.6 (30.05)	522.4 (33.73)
Median	674.0	464.0	419.5	455.0	483.0
Min, Max	310, 974	227, 765	306, 672	227, 765	227, 974
Aspartate Aminotransferase (U/L)					
n	8	19	6	25	33
Mean (SE)	77.3 (8.40)	147.9 (37.88)	205.7 (68.30)	161.8 (32.81)	141.3 (25.62)
Median	65.5	94.0	164.5	97.0	94.0
Min, Max	51, 114	28, 672	57, 521	28, 672	28, 672
Alanine Aminotransferase (U/L)					
n	8	19	6	25	33
Mean (SE)	56.1 (10.51)	116.0 (25.04)	152.3 (61.63)	124.7 (23.61)	108.1 (18.70)
Median	37.0	91.0	88.5	91.0	85.0
Min, Max	32, 109	13, 379	30, 438	13, 438	13, 438
Gamma Glutamyl Transferase (U/L)					
n	8	19	6	25	33
Mean (SE)	17.8 (2.14)	21.9 (4.37)	50.2 (10.67)	28.7 (4.76)	26.1 (3.72)
Median	16.0	16.0	47.0	17.0	17.0
Min, Max	11, 27	6, 89	11, 83	6, 89	6, 89

Variable Statistic or Category	PFIC1 (N=8)	PFIC2			Overall (N=33)
		nt-PFIC2 (N=19)	t-PFIC2 (N=6)	Overall (N=25)	
FGF-19 (pg/mL)					
n	8	19	6	25	33
Mean (SE)	194.4 (80.31)	627.6 (208.92)	3567.9 (1220.98)	1333.3 (406.35)	1057.2 (318.76)
Median	92.3	140.9	4115.4	252.5	180.7
Min, Max	19, 700	53, 3754	39, 6944	39, 6944	19, 6944
Bilirubin (mg/dL)					
n	8	19	6	25	33
Mean (SE)	5.45 (1.814)	1.81 (0.409)	2.87 (0.610)	2.06 (0.350)	2.88 (0.557)
Median	2.95	1.20	2.90	1.60	1.80
Min, Max	0.9, 15.1	0.1, 6.5	1.1, 4.5	0.1, 6.5	0.1, 15.1
Direct Bilirubin (mg/dL)					
n	8	19	6	25	33
Mean (SE)	4.038 (1.2978)	1.387 (0.3056)	2.300 (0.5310)	1.606 (0.2715)	2.195 (0.4063)
Median	2.150	1.000	2.050	1.300	1.300
Min, Max	0.70, 10.00	0.05, 4.60	0.90, 3.90	0.05, 4.60	0.05, 10.00
Cholesterol (mg/dL)					
n	8	19	6	25	33
Mean (SE)	112.9 (8.21)	193.3 (12.02)	233.5 (18.97)	202.9 (10.62)	181.1 (10.68)
Median	111.5	196.0	231.0	196.0	189.0
Min, Max	79, 155	105, 269	187, 282	105, 282	79, 282
Triglycerides (mg/dL)					
n	8	19	6	25	33
Mean (SE)	124.5 (11.06)	175.2 (18.71)	200.7 (26.50)	181.3 (15.48)	167.5 (12.69)
Median	133.0	170.0	200.5	181.0	158.0
Min, Max	64, 162	44, 409	121, 279	44, 409	44, 409
7α hydroxyl-4-cholesten-3-one (ng/mL)					
n	8	19	6	25	33
Mean (SE)	2.71 (0.774)	2.76 (0.456)	10.50 (7.442)	4.62 (1.828)	4.16 (1.397)
Median	2.45	2.30	3.70	2.70	2.70
Min, Max	0.2, 5.8	0.2, 7.7	0.2, 47.3	0.2, 47.3	0.2, 47.3

Variable Statistic or Category	PFIC1 (N=8)	PFIC2			Overall (N=33)
		nt-PFIC2 (N=19)	t-PFIC2 (N=6)	Overall (N=25)	
Retinol (µg/dL)					
n	8	19	6	25	33
Mean (SE)	73.45 (12.722)	51.41 (4.943)	39.60 (9.676)	48.58 (4.435)	54.61 (4.828)
Median	73.50	46.00	38.65	43.00	46.00
Min, Max	17.2, 119.0	17.2, 89.0	14.3, 83.0	14.3, 89.0	14.3, 119.0
25-Hydroxyvitamin D (ng/mL)					
n	8	18	5	23	31
Mean (SE)	37.88 (6.129)	28.58 (2.459)	23.48 (5.992)	27.47 (2.297)	30.16 (2.413)
Median	39.54	29.00	22.04	29.00	29.00
Min, Max	10.0, 66.9	11.6, 52.0	9.2, 40.9	9.2, 52.0	9.2, 66.9
Alpha Tocopherol (mg/dL)					
n	8	19	6	25	33
Mean (SE)	0.343 (0.0591)	0.418 (0.0636)	0.703 (0.1994)	0.486 (0.0701)	0.452 (0.0556)
Median	0.353	0.461	0.615	0.461	0.430
Min, Max	0.12, 0.65	0.04, 0.95	0.09, 1.31	0.04, 1.31	0.04, 1.31
International Normalized Ratio					
n	8	19	6	25	33
Mean (SE)	1.08 (0.031)	1.21 (0.089)	1.10 (0.052)	1.18 (0.069)	1.16 (0.053)
Median	1.05	1.10	1.10	1.10	1.10
Min, Max	1.0, 1.2	0.9, 2.7	0.9, 1.3	0.9, 2.7	0.9, 2.7

Source: Appendix 8.1, Table 14.1.4
Abbreviations: LLOQ = lower limit of quantitation; Max = maximum; Min = minimum; n = number in a given category; N = number of participants; nt-PFIC2 = non-truncating PFIC2; PFIC = progressive familial intrahepatic cholestasis; SE = standard error of the mean; t-PFIC2 = truncating PFIC2; ULOQ = upper limit of quantitation
Note: Percentages are 100*n/N. For analysis of laboratory tests, one-half of the LLOQ is used for values reported as <LLOQ or ≤LLOQ; the ULOQ is used for values reported as >ULOQ or ≥ULOQ.

4.4.3. Medical History and Concurrent Illnesses

The medical history for all enrolled participants is provided in Appendix 8.2, Listing 16.4.2.

4.5. Prior, Concomitant, and Post-intervention Therapy

Prior and concomitant medications for all enrolled participants are provided in Appendix 8.2, Listing 16.4.4.

4.6. Exposure and Study Intervention Compliance

4.6.1. Exposure

During the study period, the mean (SE) daily dose for the overall study population was 292.6 (14.52) µg/kg/day, and mean (SE) treatment duration was 1,019.0 (121.92) days (Table 4-6). Within each dose (280 µg/kg/day QD or 280 µg/kg/day BID), mean daily dose was similar in participants with PFIC1 and PFIC2. Within each dose, participants with PFIC2 had greater total investigational product exposure and treatment duration than those with PFIC1.

All participants had a treatment duration greater than 13 weeks (86 days), 28 participants (84.8%) had a treatment duration greater than 48 weeks (322 days), 22 participants (66.7%) had a treatment duration greater than 72 weeks (490 days), and 16 participants (48.5%) had a treatment duration of at least 124 weeks (854 days). Regardless of dose, treatment duration was generally similar in participants with PFIC1 compared with participants with PFIC2. Figure 4-1 displays study drug exposure throughout the study by participants grouped by PFIC type.

Due to a misinterpretation of the automatic dose-escalation protocol by the drug supplier, 3 of the 7 participants enrolled and administered study drug at Site 001 were not titrated up to the 280 µg/kg/day dose per the protocol. This dosing error resulted in a "Serious Breach of GCP or the Trial Protocol", according to United Kingdom's regulations. Participants 001051, 001053, and 001054 were dosed on 140 µg/kg/day until Week 24 (instead of Week 8), at which time they were dose-escalated to 280 µg/kg/day (Appendix 8.1, Figure 14.3.1). As participants were only delayed in their dose escalation and received the correct dose of 280 ug/kg/day on or prior to Week 24, the overall impact to efficacy was deemed negligible for the longer-term follow-up of this final analysis. A sensitivity analysis excluding all Site 001 participants was described in SAP Amendment 2 but was removed in SAP Amendment 3. The study drug exposure listing (Appendix 8.2, Listing 16.6.2) includes the dosing information for these participants.

Table 4-6: Summary of Exposure to Investigational Product by PFIC Type and Investigational Product Dose (Safety Population)

	280 QD			280 BID			Any Dose		
Variable	**PFIC1**	**PFIC2**	**Overall**	**PFIC1**	**PFIC2**	**Overall**	**PFIC1**	**PFIC2**	**Overall**
Statistic or Category	**(N=8)**	**(N=25)**	**(N=33)**	**(N=5)**	**(N=5)**	**(N=10)**	**(N=8)**	**(N=25)**	**(N=33)**
Average daily dose (µg/kg/day)									
n	8	25	33	5	5	10	8	25	33
Mean (SE)	245.9 (10.75)	246.4 (5.79)	246.3 (5.02)	546.8 (6.16)	554.5 (0.83)	550.7 (3.20)	338.6 (33.48)	277.9 (15.13)	292.6 (14.52)
Median	261.7	257.7	258.6	553.0	554.9	553.9	343.9	258.6	261.3
Min, Max	178, 267	166, 275	166, 275	523, 556	552, 557	523, 557	232, 437	166, 444	166, 444
Total investigational product exposure (µg/kg)									
n	8	25	33	5	5	10	8	25	33
Mean (SE)	149,345.9 (21,816.73)	203,404.6 (31,967.04)	190,299.5 (24,952.61)	467,992.0 (76,339.73)	534,828.0 (62,552.52)	501,410.0 (47,839.90)	441,840.9 (116,646.01)	310,370.2 (55,852.58)	342,241.9 (50,923.42)
Median	164,682.0	147,413.0	150,367.0	540,820.0	594,300.0	545,860.0	508,417.0	147,413.0	150,367.0
Min, Max	49,413, 221,893	20,713, 546,238	20,713, 546,238	165,480, 578,340	290,360, 630,000	165,480, 630,000	49,413, 800,233	20,713, 865,753	20,713, 865,753
Treatment duration (days)									
n	8	25	33	5	5	10	8	25	33
Mean (SE)	608.0 (86.84)	786.6 (113.84)	743.3 (89.14)	856.0 (139.07)	964.0 (112.12)	910.0 (86.11)	1143.0 (246.94)	979.4 (142.13)	1019.0 (121.92)
Median	678.0	563.0	599.0	981.0	1071.0	984.5	1407.5	563.0	599.0
Min, Max	213, 873	112, 2004	112, 2004	302, 1043	526, 1132	302, 1132	213, 1881	112, 2009	112, 2009

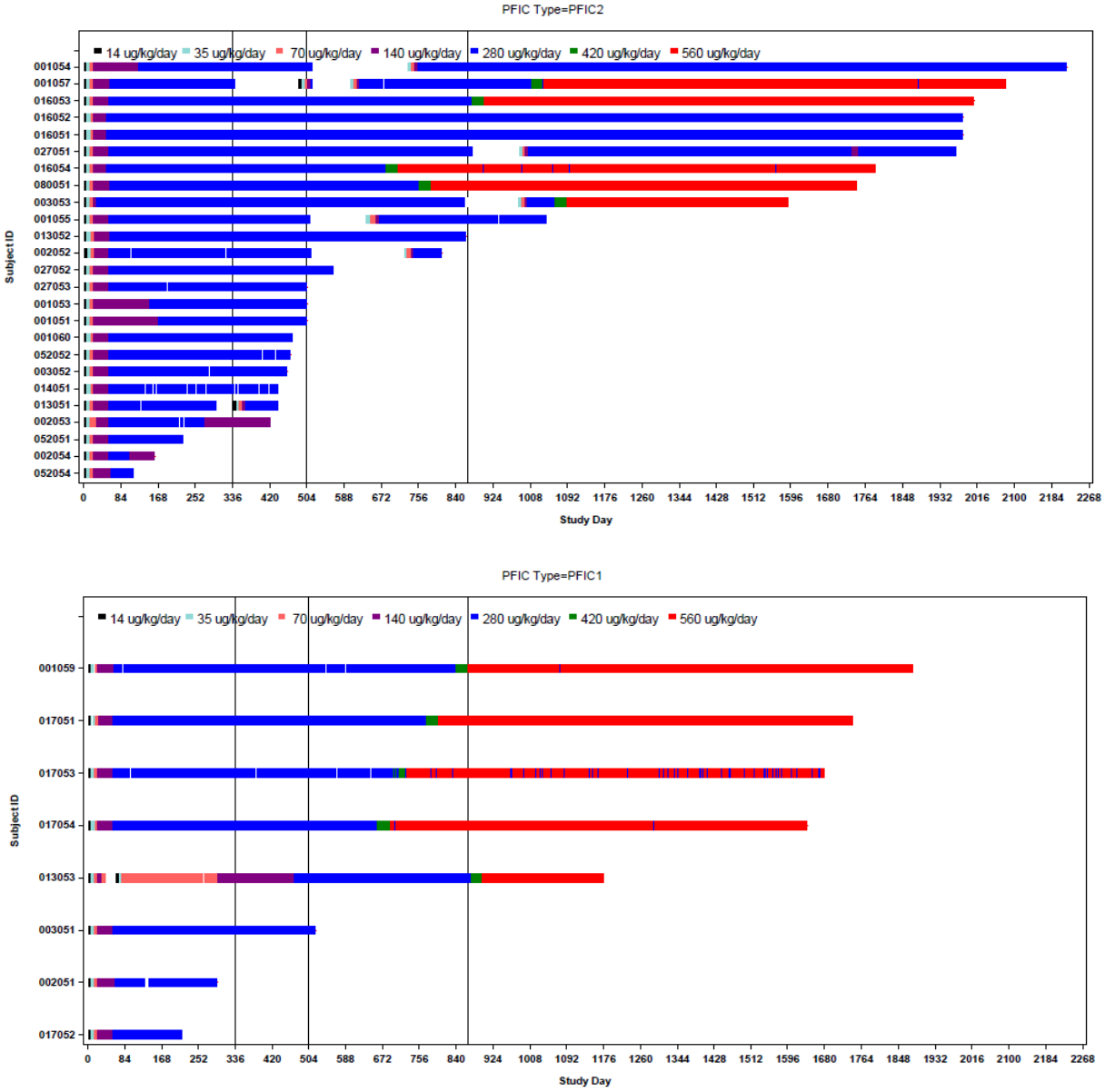
Variable Statistic or Category	280 QD PFIC1 (N=8)	280 QD PFIC2 (N=25)	280 QD Overall (N=33)	280 BID PFIC1 (N=5)	280 BID PFIC2 (N=5)	280 BID Overall (N=10)	Any Dose PFIC1 (N=8)	Any Dose PFIC2 (N=25)	Any Dose Overall (N=33)
Treatment duration (days) n (%)									
≤13 weeks (≤86 days)	0	0	0	0	0	0	0	0	0
>13 weeks (>86 days)	8 (100.0)	25 (100.0)	33 (100.0)	5 (100.0)	5 (100.0)	10 (100.0)	8 (100.0)	25 (100.0)	33 (100.0)
>48 weeks (>322 days)	6 (75.0)	22 (88.0)	28 (84.8)	4 (80.0)	5 (100.0)	9 (90.0)	6 (75.0)	22 (88.0)	28 (84.8)
>72 weeks (>490 days)	6 (75.0)	16 (64.0)	22 (66.7)	4 (80.0)	5 (100.0)	9 (90.0)	6 (75.0)	16 (64.0)	22 (66.7)
≥124 weeks (≥854 days)	1 (12.5)	9 (36.0)	10 (30.3)	4 (80.0)	4 (80.0)	8 (80.0)	5 (62.5)	11 (44.0)	16 (48.5)

Source: Appendix 8.1, Table 14.3.1

Abbreviations: BID = twice daily; max = maximum; min = minimum; n = number in a given category; N = number of participants; PFIC = progressive familial intrahepatic cholestasis; QD = once daily; SE = standard error of the mean

Note: Investigational product exposure estimates exclude dosing gaps due to participant being off study (between protocol amendments). The 280 QD dose includes all QD doses ≤280 µg/kg. The 280 BID dose includes the dose of 420 µg/kg daily for 2 weeks as part of a dose-escalation.

Figure 4-1: Study Drug Exposure Over Time by Participant (Safety Population)



Source: Appendix 8.1, Figure 14.3.1
Abbreviations: ID = identification; PFIC = progressive familial intrahepatic cholestasis
Note: Treatment information was based on actual dose received. The participants are sorted by descending order of overall treatment duration within each PFIC type. Gaps in line segments indicate drug interruption or missed doses. Vertical reference lines at Study Days 336 (Week 48), 504 (Week 72), and 868 (Week 124).

4.6.2. Dose Modification

Study drug dosing for each individual participant is found in Appendix 8.2, Listing 16.6.2.

4.6.3. Measurement of Study Intervention Compliance

Table 4-7 summarizes treatment compliance during the study. Mean (SE) compliance for the overall study population was 98.94 (0.771)% during Weeks 0-13, 97.96 (1.041)% during Weeks 14-72, 99.80 (0.099)% during Weeks 72-124, and 99.97 (0.019)% for Week 124 and onwards. Over the duration of the whole study, mean (SE) compliance was 98.95 (0.348)%.

Table 4-7: Study Drug Compliance (Safety Population)

	PFIC Type		
Study Phase Statistic	**PFIC1 (N=8)**	**PFIC2 (N=25)**	**Overall (N=33)**
Weeks 0-13 n (%)			
n	8	25	33
Mean (SE)	96.03 (3.094)	99.87 (0.073)	98.94 (0.771)
Median	100.00	100.00	100.00
Min, Max	74.7, 100.0	98.9, 100.0	74.7, 100.0
Weeks 14-72 n (%)			
n	8	25	33
Mean (SE)	99.17 (0.332)	97.57 (1.368)	97.96 (1.041)
Median	99.39	99.77	99.76
Min, Max	97.1, 100.0	66.8, 100.0	66.8, 100.0
Weeks 73-124 n (%)			
n	5	13	18
Mean (SE)	99.44 (0.311)	99.94 (0.031)	99.80 (0.099)
Median	99.73	100.00	100.00
Min, Max	98.4, 100.0	99.7, 100.0	98.4, 100.0
Weeks >124 n (%)			
n	5	9	14
Mean (SE)	99.96 (0.038)	99.98 (0.023)	99.97 (0.019)
Median	100.00	100.00	100.00
Min, Max	99.8, 100.0	99.8, 100.0	99.8, 100.0

Study Phase Statistic	PFIC Type PFIC1 (N=8)	PFIC Type PFIC2 (N=25)	Overall (N=33)
Overall (Weeks 0-EOT) n (%)			
n	8	25	33
Mean (SE)	99.24 (0.308)	98.86 (0.451)	98.95 (0.348)
Median	99.53	99.79	99.78
Min, Max	97.8, 100.0	91.6, 100.0	91.6, 100.0

Source: Appendix 8.1, Table 14.1.6

Abbreviations: EOT = end of treatment; Max = maximum; Min = minimum; n = number in a given category; N = number of participants; PFIC = progressive familial intrahepatic cholestasis; SE = standard error of the mean

Note: Compliance (%) = 100* (Number of days at least 1 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 at least 1 dose was taken = Expected treatment duration (days) - Number of days study drug was not taken (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. Compliance was not derived for participants terminated prior to the specified study phase.

5. EVALUATION OF RESPONSE TO STUDY INTERVENTION

5.1. Efficacy

The results of the final analyses described in the SAP are presented in this CSR addendum.

5.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint concerned data through Week 13 and was previously addressed in the LUM001-501 Final CSR.

5.1.2. Secondary Efficacy Endpoints

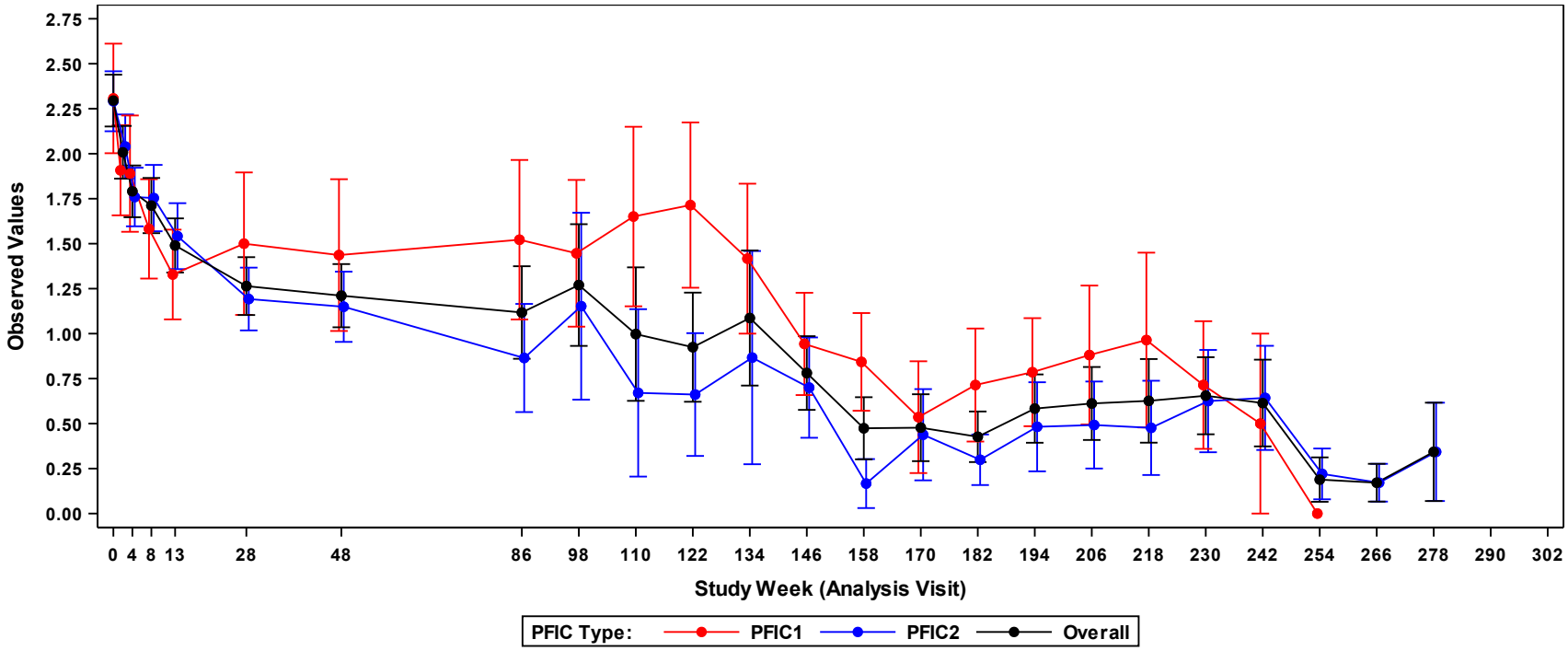
The secondary efficacy endpoints also concerned data through Week 13 and were previously addressed in the LUM001-501 Final CSR.

5.1.3. Other Efficacy Endpoints Evaluations

5.1.3.1. Changes From Baseline in Pruritus

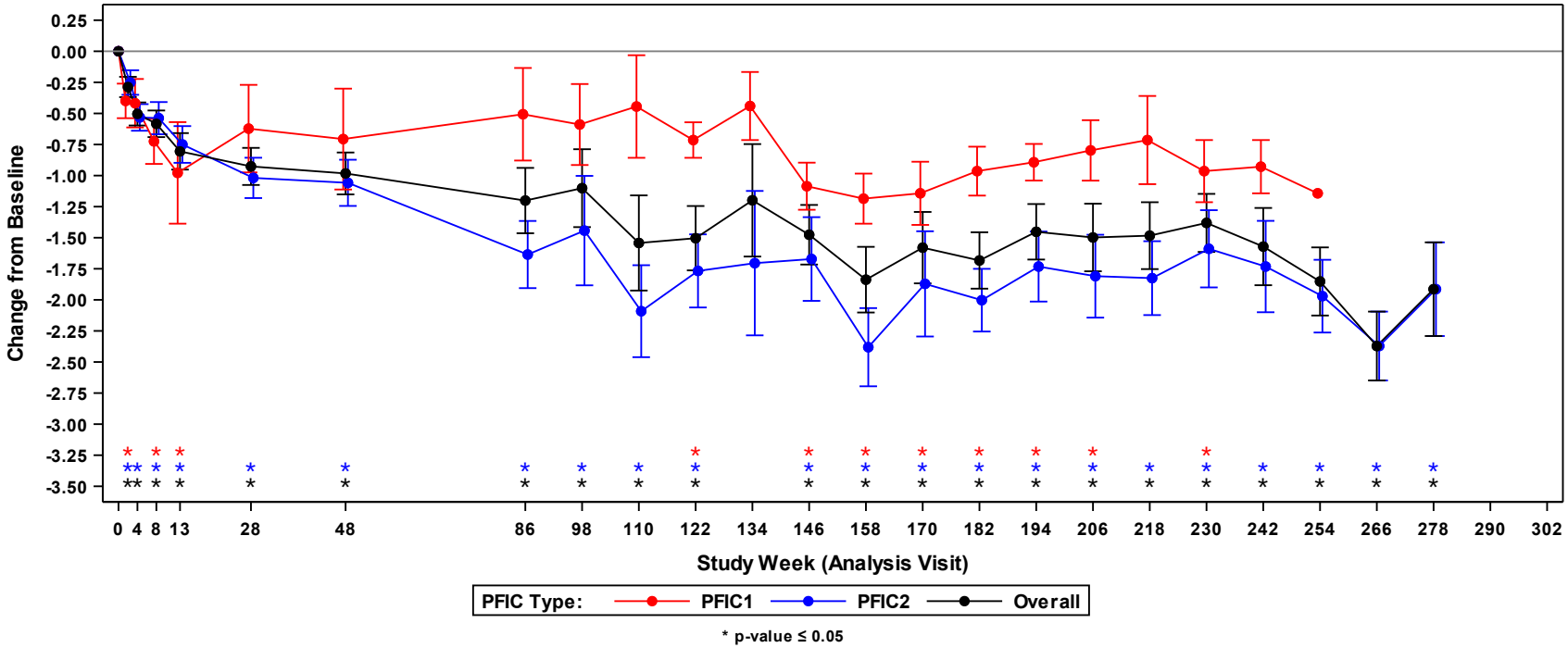
Changes from baseline in ItchoRO(Obs) weekly morning average score during the study are summarized in Table 5-1. The mean (SE) ItchoRO(Obs) weekly morning average score and the CFB for the duration of the study is presented in Figure 5-1 and Figure 5-2, respectively. A gradual numerical reduction (improvement) from baseline was observed in mean ItchoRO(Obs) weekly morning average score in the overall study population, with statistically significant reductions from baseline recorded at all analysis visits for which data were available, with the exception of Week 134. Reductions from baseline were statistically significant at Weeks 146 through 230 for participants with PFIC1 and PFIC2 (with the exception of Week 218 for participants with PFIC1) (Appendix 8.1, Table 14.2.3.2.1). An initial reduction to Week 13 in mean ItchoRO(Obs) weekly morning average score was observed in all participants, followed by a short period where the mean score stabilized, at a level significantly reduced from baseline. A second reduction from Week 98 and Week 122 was seen for participants with PFIC2 and PFIC1, respectively. The CFB was more pronounced in participants with PFIC2 than those with PFIC1. Participants with nt-PFIC2 showed a particularly encouraging response; reductions from baseline were statistically significant for all analysis visits, with the exception of Week 134 (which included data for 2 participants) (Appendix 8.1, Table 14.2.3.2.2).

Figure 5-1: Mean (SE) ItchRO(Obs) Weekly Morning Average Score by PFIC Type Over Time (Intent-to-Treat Population)



Source: Appendix 8.1, Figure 14.2.3.2.1.2
Abbreviations: ItchRO(Obs) = Itch Reported Outcome (Observer); PFIC = progressive familial intrahepatic cholestasis; SE = standard error of the mean
Note: Baseline was defined as the average of daily scores in the week consisting of the 7 days immediately before the first dose. Only analysis visits with an overall n ≥4 were summarized. Participants that did not complete at least 1 post-Week 72 assessment were excluded from all post-Week 72 analyses. Participants that did not complete at least 1 post-Week 124 assessment were excluded from all post-Week 124 analyses.

Figure 5-2: Mean (SE) Change From Baseline in ItchRO(Obs) Weekly Morning Average Score by PFIC Type Over Time (Intent-to-Treat Population)



Source: Appendix 8.1, Figure 14.2.3.2.1.1

Abbreviations: CFB = change from baseline; ItchRO(Obs) = Itch Reported Outcome (Observer); PFIC = progressive familial intrahepatic cholestasis; SE = standard error of the mean

Note: Baseline was defined as the average of daily scores in the week consisting of the 7 days immediately before the first dose. Only analysis visits with an overall n ≥4 were summarized. Participants that did not complete at least 1 post-Week 72 assessment were excluded from all post-Week 72 analyses. Participants that did not complete at least 1 post-Week 124 assessment were excluded from all post-Week 124 analyses. * Paired t-test used to test if mean change is statistically significant (null hypothesis is that the mean CFB is equal to zero).

Table 5-1: Change From Baseline in ItchRO(Obs) Weekly Morning Average Score by PFIC Type and Analysis Visit (Intent-to-Treat Population)

			PFIC2							
	PFIC1 (N=8)		nt-PFIC2 (N=19)		t-PFIC2 (N=6)		Overall (N=25)		Overall (N=33)	
Visit Statistic	Observed	CFB	Observed	CFB	Observed	CFB	Observed	CFB	Observed	CFB
Baseline										
n	8		19		6		25		33	
Mean	2.307		2.090		2.929		2.291		2.295	
SD (SE)	0.8613 (0.3045)		0.8237 (0.1890)		0.5010 (0.2045)		0.8335 (0.1667)		0.8267 (0.1439)	
Week 48/LOCF										
n	8	8	19	19	6	6	25	25	33	33
Mean	1.363	-0.944	1.172	-0.919	2.028	-0.901	1.377	-0.914	1.374	-0.922
SD (SE)	1.0742 (0.3798)	1.4064 (0.4972)	0.9751 (0.2237)	0.9012 (0.2067)	1.2107 (0.4943)	1.0131 (0.4136)	1.0760 (0.2152)	0.9072 (0.1814)	1.0587 (0.1843)	1.0247 (0.1784)
p-value for CFB[a]		0.0994		0.0003		0.0813		<0.0001		<0.0001
Week 86										
n	5	5	7	7	1	1	8	8	13	13
Mean	1.522	-0.507	0.621	-1.726	2.571	-1.000	0.865	-1.635	1.117	-1.201
SD (SE)	0.9910 (0.4432)	0.8324 (0.3723)	0.5369 (0.2029)	0.7775 (0.2939)	---	---	0.8501 (0.3006)	0.7642 (0.2702)	0.9272 (0.2572)	0.9478 (0.2629)
p-value for CFB[a]		0.2451		0.0011		---		0.0005		0.0006

Visit Statistic	PFIC1 (N=8)		PFIC2						Overall (N=33)	
			nt-PFIC2 (N=19)		t-PFIC2 (N=6)		Overall (N=25)			
	Observed	CFB	Observed	CFB	Observed	CFB	Observed	CFB	Observed	CFB
Week 110										
n	3	3	4	4	2	2	6	6	9	9
Mean	1.651	-0.444	0.042	-2.458	1.929	-1.357	0.671	-2.091	0.997	-1.542
SD (SE)	0.8642 (0.4989)	0.7148 (0.4127)	0.0833 (0.0417)	0.7447 (0.3723)	1.3132 (0.9286)	0.9091 (0.6429)	1.1395 (0.4652)	0.9063 (0.3700)	1.1129 (0.3710)	1.1485 (0.3828)
p-value for CFB[a]		0.3942		0.0071		0.2816		0.0024		0.0038
Week 158										
n	5	5	6	6	0	0	6	6	11	11
Mean	0.843	-1.186	0.167	-2.381	---	---	0.167	-2.381	0.474	-1.838
SD (SE)	0.6069 (0.2714)	0.4506 (0.2015)	0.3333 (0.1361)	0.7703 (0.3145)	---	---	0.3333 (0.1361)	0.7703 (0.3145)	0.5724 (0.1726)	0.8761 (0.2642)
p-value for CFB[a]		0.0042		0.0006		---		0.0006		<0.0001
Week 206										
n	4	4	9	9	0	0	9	9	13	13
Mean	0.881	-0.798	0.492	-1.810	---	---	0.492	-1.810	0.612	-1.498
SD (SE)	0.7723 (0.3861)	0.4862 (0.2431)	0.7253 (0.2418)	1.0000 (0.3333)	---	---	0.7253 (0.2418)	1.0000 (0.3333)	0.7312 (0.2028)	0.9808 (0.2720)
p-value for CFB[a]		0.0464		0.0006		---		0.0006		0.0001

	PFIC1 (N=8)		PFIC2						Overall (N=33)	
			nt-PFIC2 (N=19)		t-PFIC2 (N=6)		Overall (N=25)			
Visit Statistic	**Observed**	**CFB**	**Observed**	**CFB**	**Observed**	**CFB**	**Observed**	**CFB**	**Observed**	**CFB**
Week 230										
n	4	4	8	8	0	0	8	8	12	12
Mean	0.714	-0.964	0.625	-1.589	---	---	0.625	-1.589	0.655	-1.381
SD (SE)	0.7095 (0.3548)	0.5000 (0.2500)	0.8043 (0.2844)	0.8788 (0.3107)	---	---	0.8043 (0.2844)	0.8788 (0.3107)	0.7422 (0.2143)	0.8089 (0.2335)
p-value for CFB[a]		0.0308		0.0014		---		0.0014		0.0001

Source: Appendix 8.1, Tables 14.2.3.2.1 and 14.2.3.2.2

Abbreviations: CFB = change from baseline, defined as post-baseline value minus baseline value; ItchRO(Obs) = Itch Reported Outcome (Observer); LOCF = last observation carried forward; n = number in a given category; N = number of participants; nt-PFIC2 = non-truncating PFIC2; PFIC = progressive familial intrahepatic cholestasis; SD = standard deviation; SE = standard error of the mean; t-PFIC2 = truncating PFIC2

Note: ItchRO scores have a range from 0 to 4, with the higher score indicating increasing itch severity. Participants that did not complete at least 1 post-Week 48 assessment were excluded from all post-Week 48 analyses, including Week 122/LOCF. Participants that did not complete at least 1 post-Week 122 assessment were excluded from all post-Week 122 analyses.

a p-value for testing if the mean CFB at the specified analysis visit is zero, using a paired t-test.

Similar results were seen across all measures of ItchRO(Obs), with smaller numerical reductions in participants with PFIC1 compared to participants with PFIC2 from baseline in ItchRO(Obs) weekly average score, weekly morning average score, and weekly evening average score (Appendix 8.1, Tables 14.2.3.1.1, 14.2.3.2.1, and 14.2.3.3).

Fewer data were available for the ItchRO(Pt) assessments than for the ItchRO(Obs) assessment. However, a similar pattern was observed, where overall, participants recorded a numerical reduction in ItchRO score, and participants with PFIC2 showed a greater decrease than those with PFIC1. These results were consistent across the weekly average (Appendix 8.1, Table 14.2.4.1), weekly morning average (Appendix 8.1, Table 14.2.4.2), and weekly evening average (Appendix 8.1, Table 14.2.4.3) data.

Long-term results presented here show a continuation of the improvement in pruritus, as shown by the CFB in ItchRO assessments presented in the LUM001-501 Final CSR.

Additionally, the percentage of days where the ItchRO(Obs) daily morning score was ≤1 point (Appendix 8.1, Table 14.2.3.2.3), and pruritus responder rates (Appendix 8.1, Tables 14.2.14.1 and 14.2.14.2) illustrate the long-term decrease in ItchRO assessments, continuing the reduction reported to Week 48/ET in the LUM001-501 Final CSR. For Weeks >204, 87.3% of participants overall reported an ItchRO(Obs) daily morning score of ≤1 point, compared with 21.6% of participants at screening/baseline. Reductions reported using these measures were consistent in showing greater reductions to Week 124 in participants with PFIC2 than those with PFIC1; differences between participants with PFIC2 and PFIC1 diminished after this analysis visit.

5.1.3.2. Change From Baseline in the CSS

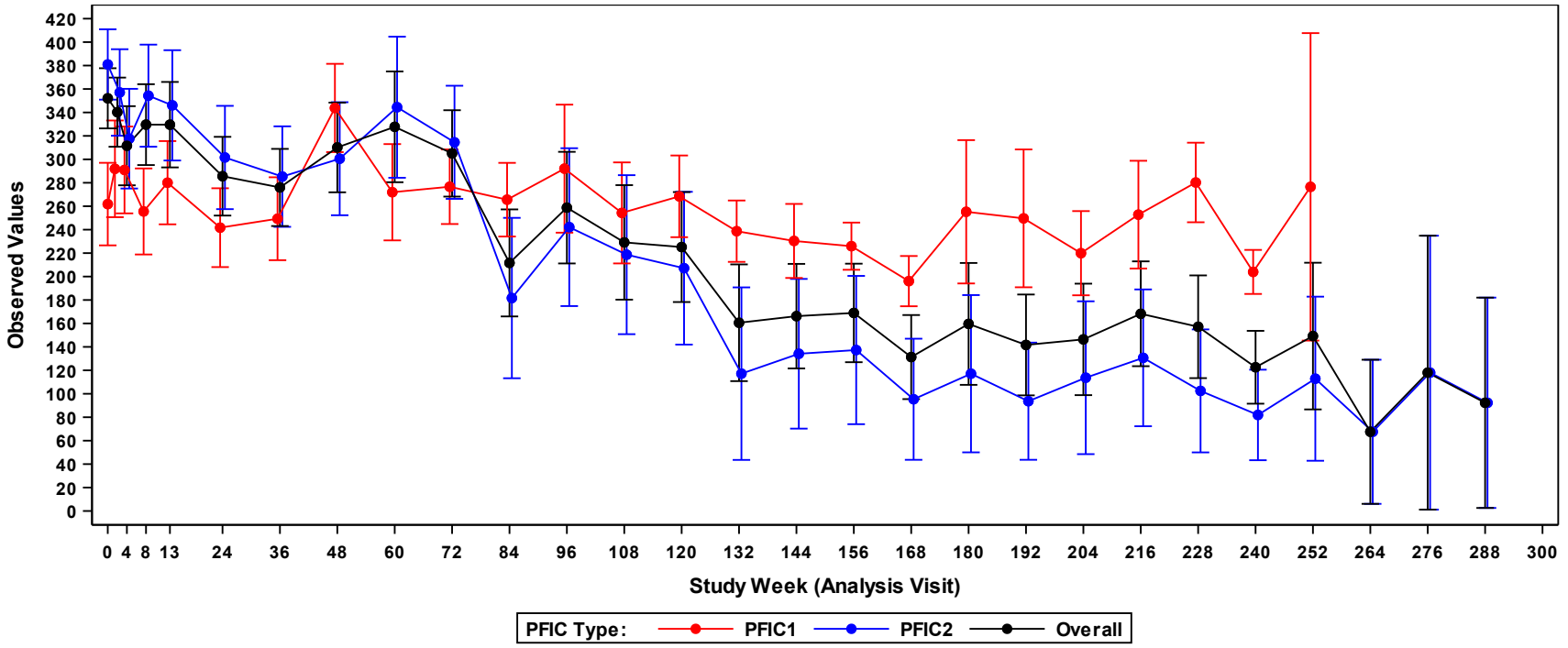
Appendix 8.2, Listing 16.7.2 provides by-participant CSS scores, with a summary of CFB in CSS scores provided in Appendix 8.1, Table 14.2.15.

5.1.3.3. Changes From Baseline in sBA, ALT, AST, and Total and Direct Bilirubin

During the study, a numerical reduction in mean sBA levels from baseline was evident for participants with PFIC2 (Figure 5-3, Figure 5-4, and Table 5-2). Following an initial reduction and then return to near baseline at Week 60, a sustained reduction from baseline was noted from Week 72, before levelling off at Week 132. Overall, for participants with PFIC2, sBA levels decreased (improved) over time, with statistically significant decreases from baseline at Week 36, and at Weeks 132 to 240 (Appendix 8.1, Table 14.2.2.1). These reductions were more pronounced in participants with nt-PFIC2, than those with t-PFIC2; statistically significant reductions from baseline were observed at Weeks 2, 4, 36, 108, and 120 through 240 in participants with nt-PFIC2, whereas no statistically significant reductions from baseline were observed for participants with t-PFIC2 (Appendix 8.1, Table 14.2.2.2). This shows continued improvement in sBA levels from Week 13 and Week 72, as reported in the LUM001-501 Final CSR for participants with PFIC2 (Figure 5-3). For participants with PFIC1, no such sustained numerical reduction was evident, although the small sample size (n = 8) should be considered. No statistically significant changes from baseline were observed for participants with PFIC1, with reductions in sBA levels from baseline noted at only 6 of the 24 analysis visits for which data were available (Appendix 8.1, Table 14.2.2.1).

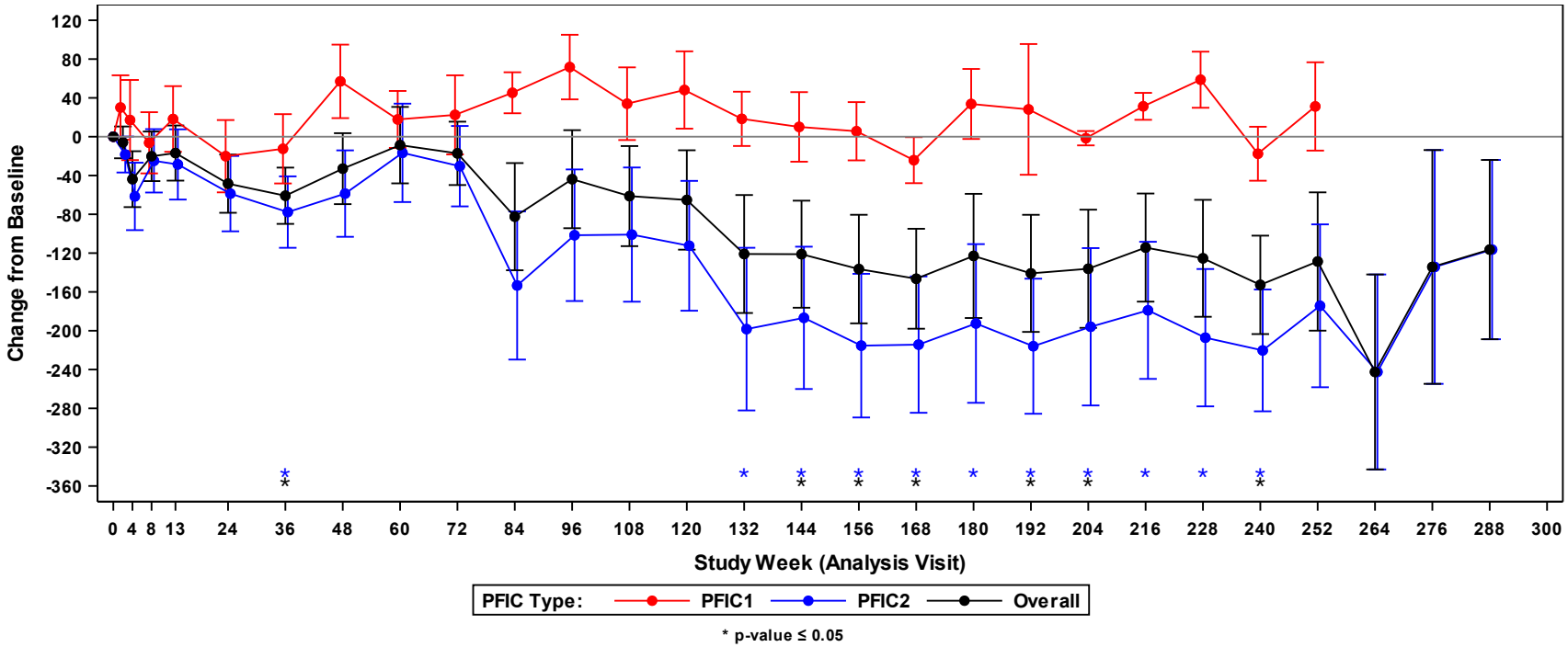
The responder analysis also showed a greater response from participants with PFIC2 compared to those with PFIC1; at least 62.5% of participants with PFIC2 showed a % CFB of ≤-75 or sBA ≤102 µmol/L for all analysis visits from Week 132 to 240. In comparison, no participant with PFIC1 was classified as a responder after Week 13 (Appendix 8.1, Table 14.2.14.3).

Figure 5-3: Mean (SE) Serum Bile Acid (µmol/L) by PFIC Type Over Time (Intent-to-Treat Population)



Source: Appendix 8.1, Figure 14.2.2.1.2
Abbreviations: PFIC = progressive familial intrahepatic cholestasis; SE = standard error of the mean
Note: Baseline was defined as the last observation obtained before the first dose. Only analysis visits with an overall n ≥4 were summarized. Participants that did not complete at least 1 post-Week 72 assessment were excluded from all post-Week 72 analyses. Participants that did not complete at least 1 post-Week 124 assessment were excluded from all post-Week 124 analyses.

Figure 5-4: Mean (SE) Change From Baseline in Serum Bile Acid Level (µmol/L) by PFIC Type (Intent-to-Treat Population)



Source: Appendix 8.1, Figure 14.2.2.1.1
Abbreviations: CFB = change from baseline; PFIC = progressive familial intrahepatic cholestasis; SE = standard error of the mean
Note: Baseline was defined as the last observation obtained before the first dose. Only analysis visits with an overall n ≥4 were summarized. Participants that did not complete at least 1 post-Week 72 assessment were excluded from all post-Week 72 analyses. Participants that did not complete at least 1 post-Week 124 assessment were excluded from all post-Week 124 analyses. * Paired t-test used to test if mean change is statistically significant (null hypothesis is that the mean CFB is equal to zero).

Table 5-2: Serum Bile Acid (µmol/L) Level – Change From Baseline Over Time

	PFIC1 (N=8)		PFIC2						Overall (N=33)	
			nt-PFIC2 (N=19)		t-PFIC2 (N=6)		Overall (N=25)			
Visit / Statistic	Observed	CFB	Observed	CFB	Observed	CFB	Observed	CFB	Observed	CFB
Baseline										
n	8		19		6		25		33	
Mean	261.81		373.35		404.92		380.93		352.05	
SD (SE)	99.574 (35.205)		161.950 (37.154)		112.398 (45.886)		149.974 (29.995)		147.395 (25.658)	
Week 72/LOCF										
n	8	8	19	19	6	6	25	25	33	33
Mean	284.30	22.49	351.19	-22.16	433.36	28.44	370.91	-10.02	349.91	-2.14
SD (SE)	84.455 (29.859)	84.474 (29.866)	234.904 (53.891)	175.593 (40.284)	154.473 (63.063)	81.243 (33.167)	218.263 (43.653)	158.071 (31.614)	196.749 (34.250)	143.181 (24.925)
p-value for CFB[a]		0.4760		0.5890		0.4304		0.7541		0.9322

	PFIC1 (N=8)		PFIC2						Overall (N=33)	
			nt-PFIC2 (N=19)		t-PFIC2 (N=6)		Overall (N=25)			
Visit Statistic	**Observed**	**CFB**	**Observed**	**CFB**	**Observed**	**CFB**	**Observed**	**CFB**	**Observed**	**CFB**
Week 96										
n	5	5	8	8	2	2	10	10	15	15
Mean	292.05	71.75	188.03	-142.54	458.61	62.32	242.14	-101.57	258.78	-43.80
SD (SE)	122.104 (54.606)	74.421 (33.282)	201.167 (71.123)	221.726 (78.392)	87.427 (61.820)	51.470 (36.395)	212.933 (67.335)	214.459 (67.818)	184.392 (47.610)	195.707 (50.531)
p-value for CFB[a]		0.0974		0.1118		0.3365		0.1684		0.4007
Week 120										
n	5	5	9	9	3	3	12	12	17	17
Mean	268.42	48.12	116.10	-193.53	480.19	130.78	207.13	-112.45	225.15	-65.23
SD (SE)	77.933 (34.853)	89.108 (39.850)	169.055 (56.352)	209.271 (69.757)	129.925 (75.012)	44.930 (25.941)	225.763 (65.172)	231.798 (66.914)	193.361 (46.897)	211.217 (51.228)
p-value for CFB[a]		0.2937		0.0241		0.0372		0.1210		0.2211
Week 144										
n	5	5	9	9	1	1	10	10	15	15
Mean	230.38	10.08	101.33	-208.31	429.29	7.57	134.12	-186.72	166.21	-121.12
SD (SE)	70.593 (31.570)	80.195 (35.864)	183.757 (61.252)	235.106 (78.369)	---	---	201.918 (63.852)	231.934 (73.344)	172.741 (44.602)	213.635 (55.160)
p-value for CFB[a]		0.7927		0.0289		---		0.0314		0.0455

	PFIC1 (N=8)		PFIC2						Overall (N=33)	
			nt-PFIC2 (N=19)		t-PFIC2 (N=6)		Overall (N=25)			
Visit Statistic	**Observed**	**CFB**	**Observed**	**CFB**	**Observed**	**CFB**	**Observed**	**CFB**	**Observed**	**CFB**
Week 168										
n	5	5	9	9	0	0	9	9	14	14
Mean	196.10	-24.20	95.32	-214.31	---	---	95.32	-214.31	131.31	-146.42
SD (SE)	47.921 (21.431)	53.043 (23.722)	154.972 (51.657)	210.788 (70.263)	---	---	154.972 (51.657)	210.788 (70.263)	134.152 (35.854)	192.728 (51.509)
p-value for CFB[a]		0.3653		0.0158		---		0.0158		0.0139
Week 192										
n	4	4	9	9	0	0	9	9	13	13
Mean	249.64	28.13	93.66	-215.97	---	---	93.66	-215.97	141.65	-140.87
SD (SE)	117.576 (58.788)	134.740 (67.370)	149.948 (49.983)	208.821 (69.607)	---	---	149.948 (49.983)	208.821 (69.607)	155.113 (43.021)	217.624 (60.358)
p-value for CFB[a]		0.7044		0.0146		---		0.0146		0.0378
Week 216										
n	4	4	9	9	0	0	9	9	13	13
Mean	252.79	31.28	130.65	-178.98	---	---	130.65	-178.98	168.23	-114.28
SD (SE)	91.948 (45.974)	27.750 (13.875)	175.073 (58.358)	211.989 (70.663)	---	---	175.073 (58.358)	211.989 (70.663)	161.214 (44.713)	200.884 (55.715)
p-value for CFB[a]		0.1095		0.0351		---		0.0351		0.0627

			PFIC2							
	PFIC1 (N=8)		nt-PFIC2 (N=19)		t-PFIC2 (N=6)		Overall (N=25)		Overall (N=33)	
Visit Statistic	Observed	CFB	Observed	CFB	Observed	CFB	Observed	CFB	Observed	CFB
Week 240										
n	4	4	8	8	0	0	8	8	12	12
Mean	203.95	-17.57	81.93	-220.29	---	---	81.93	-220.29	122.60	-152.71
SD (SE)	37.571 (18.786)	55.638 (27.819)	109.218 (38.614)	177.565 (62.779)	---	---	109.218 (38.614)	177.565 (62.779)	107.634 (31.071)	175.702 (50.721)
p-value for CFB[a]		0.5726		0.0099		---		0.0099		0.0118

Source: Appendix 8.1, Tables 14.2.2.1 and 14.2.2.2

Abbreviations: CFB = change from baseline, defined as post-baseline value minus baseline value; LOCF = last observation carried forward; n = number in a given category; N = number of participants; nt-PFIC2 = non-truncating PFIC2; PFIC = progressive familial intrahepatic cholestasis; t-PFIC2 = truncating PFIC2; SD = standard deviation; SE = standard error of the mean

Note: Participants that did not complete at least 1 post-Week 72 assessment were excluded from all post-Week 72 analyses, including Week 124/LOCF. Participants that did not complete at least 1 post-Week 124 assessment were excluded from all post-Week 124 analyses.

a p-value for testing if the mean CFB at the specified analysis visit is zero, using a paired t-test.

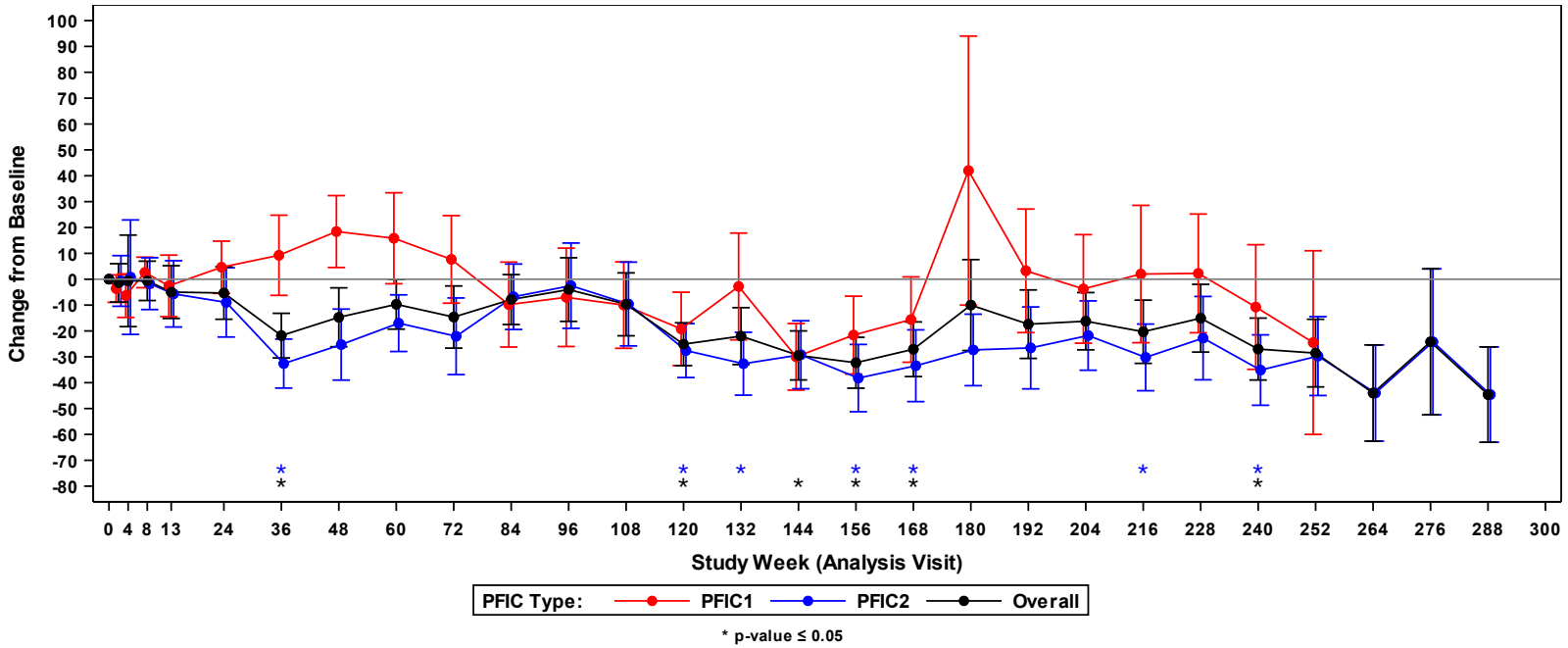
During the study, numerical reductions (improvement) in mean ALT concentrations from baseline were observed in the overall study population (Figure 5-5) Despite an initial increase in ALT concentration in participants with PFIC1, a numerical reduction was observed from Weeks 84 to 168; after this point, the sample size was reduced to <5 participants, and the effect was lessened. Participants with PFIC2 showed a numerical reduction (improvement) in ALT concentrations from baseline, which levelled off at Week 120. Statistically significant reductions from baseline were noted in participants with PFIC2 at Weeks 36, 120, 132, 156, 168, 216, and 240 (Appendix 8.1, Table 14.2.5.1). Overall results for PFIC2 were comparable to those for the PFIC2 subtypes (Appendix 8.1, Table 14.2.5.2). These results indicate continued improvement in ALT concentrations from Week 72 for participants with PFIC2, as reported in the LUM001-501 Final CSR, and also suggested a long-term improvement in ALT concentrations for participants with PFIC1.

Numerical reductions (improvement) in mean AST concentrations were observed during the study (Figure 5-6), but were statistically significant reduced from baseline at few analysis visits (at Weeks 120, 144, 156, and 240 for the overall study population; at Weeks 36, 48, 156, and 240 for participants with PFIC2; and at Weeks 36 and 240 for participants with nt-PFIC2; Appendix 8.1, Tables 14.2.9.1 and 14.2.9.2). Changes in AST concentration up to Week 72 were not previously reported in the LUM001-501 Final CSR; results presented here from the final analysis show sustained numerical reductions from baseline in all participants in AST concentrations, but statistically significant reductions at few of the analysis visits.

Increases (a worsening) in mean total bilirubin in participants with PFIC1 and PFIC2 reported at Week 72 in the LUM001-501 Final CSR were not sustained over the longer term (Figure 5-7). By Week 204 through Week 240 (beyond which the overall sample size dropped below 10), mean total bilirubin levels had returned to close to baseline levels (participants with PFIC2) or showed a reduction (improvement) from baseline (participants with PFIC1); however, no statistically significant reductions from baseline in total bilirubin were observed (Appendix 8.1, Tables 14.2.6.1 and 14.2.6.2).

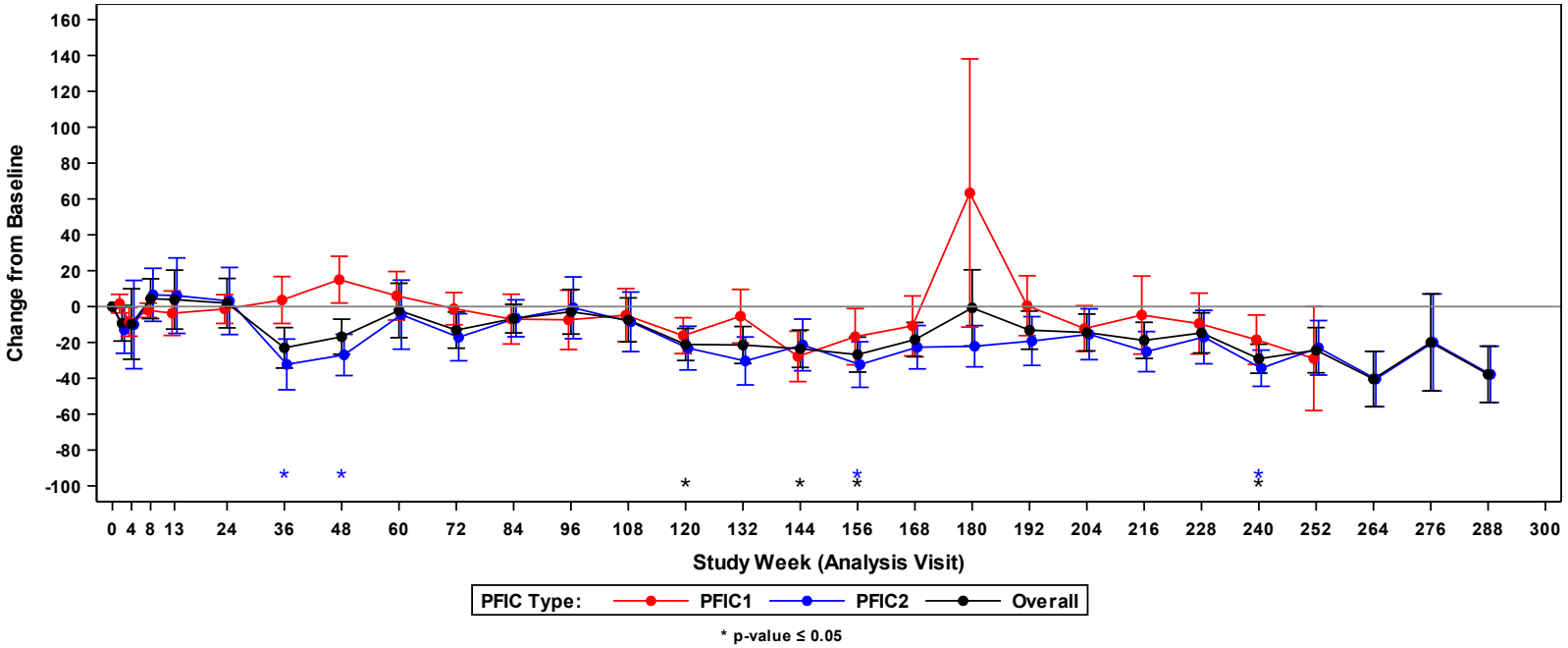
Similarly, increases (a worsening) in mean direct bilirubin in participants with PFIC1 and PFIC2 reported at Week 72 in the LUM001-501 Final CSR were not sustained over the longer term (Figure 5-8). By Week 204 and through Week 240 (beyond which the overall sample size dropped below 10), mean direct bilirubin levels showed a reduction (improvement) from baseline for participants with PFIC1 and PFIC2; however, no statistically significant reductions from baseline in direct bilirubin were observed (Appendix 8.1, Tables 14.2.7.1 and 14.2.7.2).

Figure 5-5: Mean (SE) Change From Baseline in Alanine Aminotransferase (U/L) by PFIC Type (Intent-to-Treat Population)



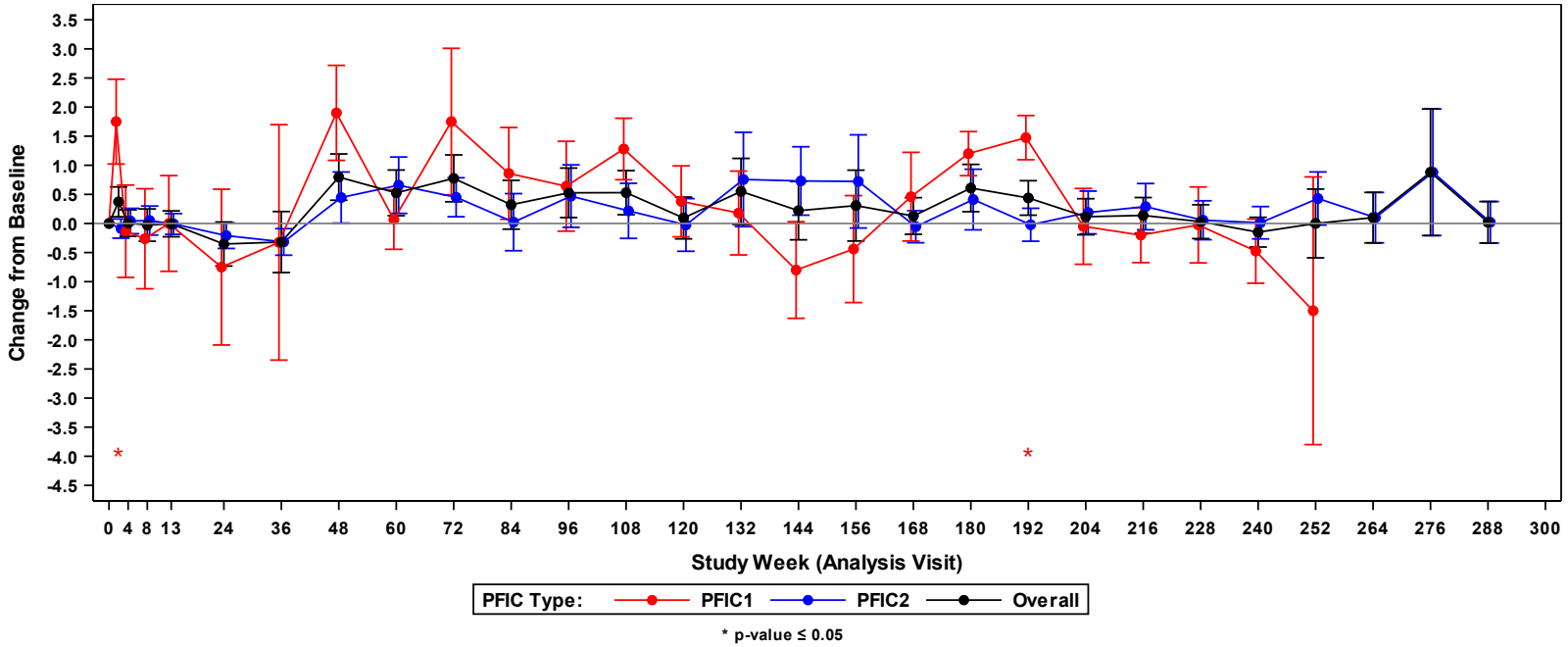
Source: Appendix 8.1, Figure 14.2.5.1
Abbreviations: CFB = change from baseline; PFIC = progressive familial intrahepatic cholestasis; SE = standard error of the mean
Note: Baseline was defined as the last observation obtained before the first dose. Only analysis visits with an overall n ≥4 were summarized. Participants that did not complete at least 1 post-Week 72 assessment were excluded from all post-Week 72 analyses. Participants that did not complete at least 1 post-Week 124 assessment were excluded from all post-Week 124 analyses. * Paired t-test used to test if mean change is statistically significant (null hypothesis is that the mean CFB is equal to zero).

Figure 5-6: Mean (SE) Change From Baseline in Aspartate Aminotransferase (U/L) by PFIC Type (Intent-to-Treat Population)



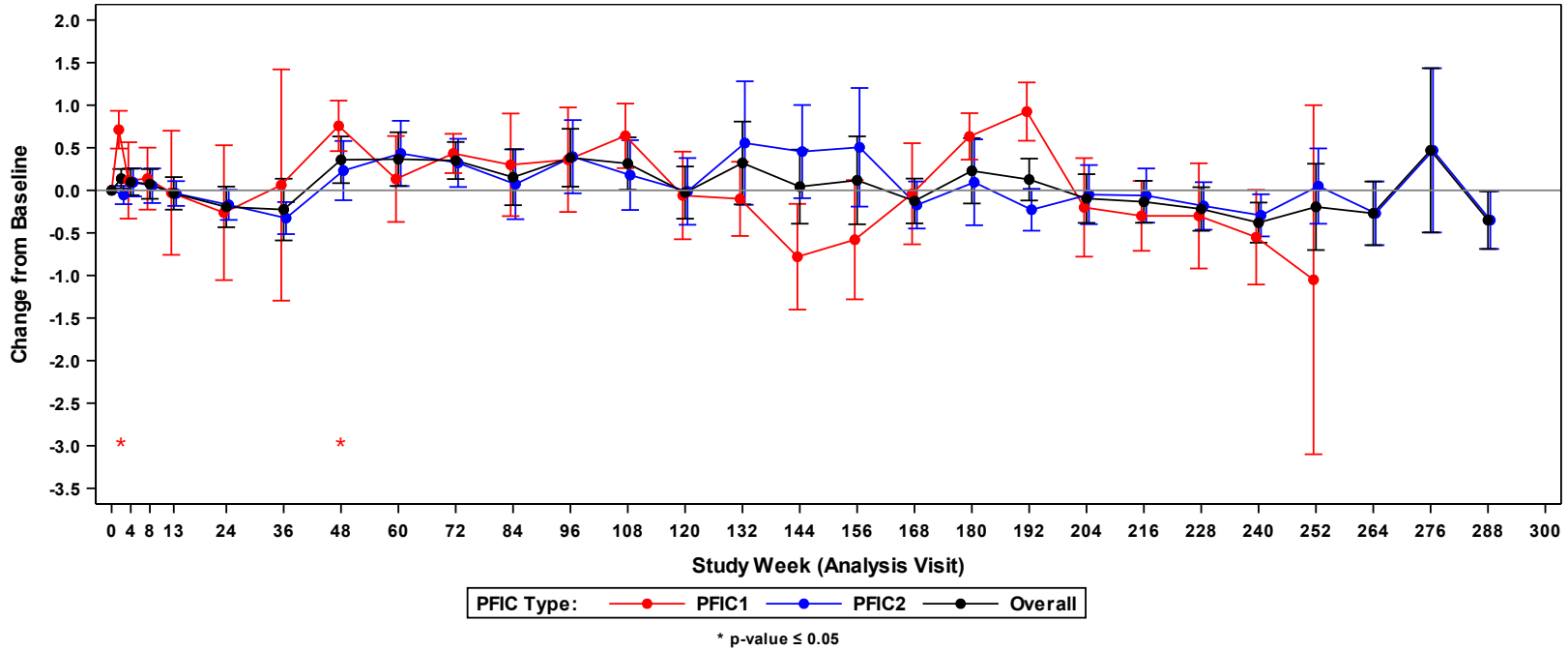
Source: Appendix 8.1, Figure 14.2.9.1
Abbreviations: CFB = change from baseline; PFIC = progressive familial intrahepatic cholestasis; SE = standard error of the mean
Note: Baseline was defined as the last observation obtained before the first dose. Only analysis visits with an overall n ≥4 were summarized. Participants that did not complete at least 1 post-Week 72 assessment were excluded from all post-Week 72 analyses. Participants that did not complete at least 1 post-Week 124 assessment were excluded from all post-Week 124 analyses. * Paired t-test used to test if mean change is statistically significant (null hypothesis is that the mean CFB is equal to zero).

Figure 5-7: Mean (SE) Change From Baseline in Total Bilirubin (mg/dL) by PFIC Type (Intent-to-Treat Population)



Source: Appendix 8.1, Figure 14.2.6.1
Abbreviations: CFB = change from baseline; PFIC = progressive familial intrahepatic cholestasis; SE = standard error of the mean
Note: Baseline was defined as the last observation obtained before the first dose. Only analysis visits with an overall n ≥4 were summarized. Participants that did not complete at least 1 post-Week 72 assessment were excluded from all post-Week 72 analyses. Participants that did not complete at least 1 post-Week 124 assessment were excluded from all post-Week 124 analyses. * Paired t-test used to test if mean change is statistically significant (null hypothesis is that the mean CFB is equal to zero).

Figure 5-8: Mean (SE) Change From Baseline in Direct Bilirubin (mg/dL) by PFIC Type (Intent-to-Treat Population)



Source: Appendix 8.1, Figure 14.2.7.1
Abbreviations: CFB = change from baseline; PFIC = progressive familial intrahepatic cholestasis; SE = standard error of the mean
Note: For concentrations reported as above the maximum quantitation limit (10 mg/dL), the maximum quantitation limit was used as the analysis value. Baseline was defined as the last observation obtained before the first dose. Only analysis visits with an overall n ≥4 were summarized. Participants that did not complete at least 1 post-Week 72 assessment were excluded from all post-Week 72 analyses. Participants that did not complete at least 1 post-Week 124 assessment were excluded from all post-Week 124 analyses. * Paired t-test used to test if mean change is statistically significant (null hypothesis is that the mean CFB is equal to zero).

Changes from baseline for analysis visits from baseline to Week 124/LOCF in sBA, ALT, AST, total bilirubin, and direct bilirubin are presented in Appendix 8.1, Table 14.2.1.

Responder analyses, in general, indicated a better response from participants with PFIC2 than in those with PFIC1. A greater percentage of participants with PFIC2 compared with PFIC1 were classified as responders, defined as a shift from >ULN at baseline to normal in AST, ALT and total bilirubin (Appendix 8.1, Table 14.2.14.4).

5.1.3.4. Change From Baseline in ALP, C4, Total Cholesterol, LDL-C, and GGT

Changes from baseline to EOT are presented for ALP (Appendix 8.1, Tables 14.2.8.1 and 14.2.8.2), C4 (Appendix 8.1, Tables 14.2.11.1 and 14.2.11.2), total cholesterol (Appendix 8.1, Tables 14.2.10.1 and 14.2.10.2), LDL-C (Appendix 8.1, Tables 14.2.13.1 and 14.2.13.2), and GGT (Appendix 8.1, Tables 14.2.12.1 and 14.2.12.2). Change from baseline in C4 is also presented graphically (Appendix 8.1, Figure 14.2.11.1). A responder analysis for C4 is included in Appendix 8.1, Table 14.2.14.4.

5.1.3.5. Change From Baseline for PedsQL Total Scale Score (Parent), Multidimensional Fatigue Scale Score (Parent), and Family Impact Total Scale Score

Summaries of changes from baseline in the PedsQL questionnaire are reported in Appendix 8.1, for the Total Scale Score (parent) (Table 14.2.17.1), Multidimensional Fatigue Scale Score (parent) (Table 14.2.17.2), and the Family Impact Total Scale Score (Table 14.2.17.3).

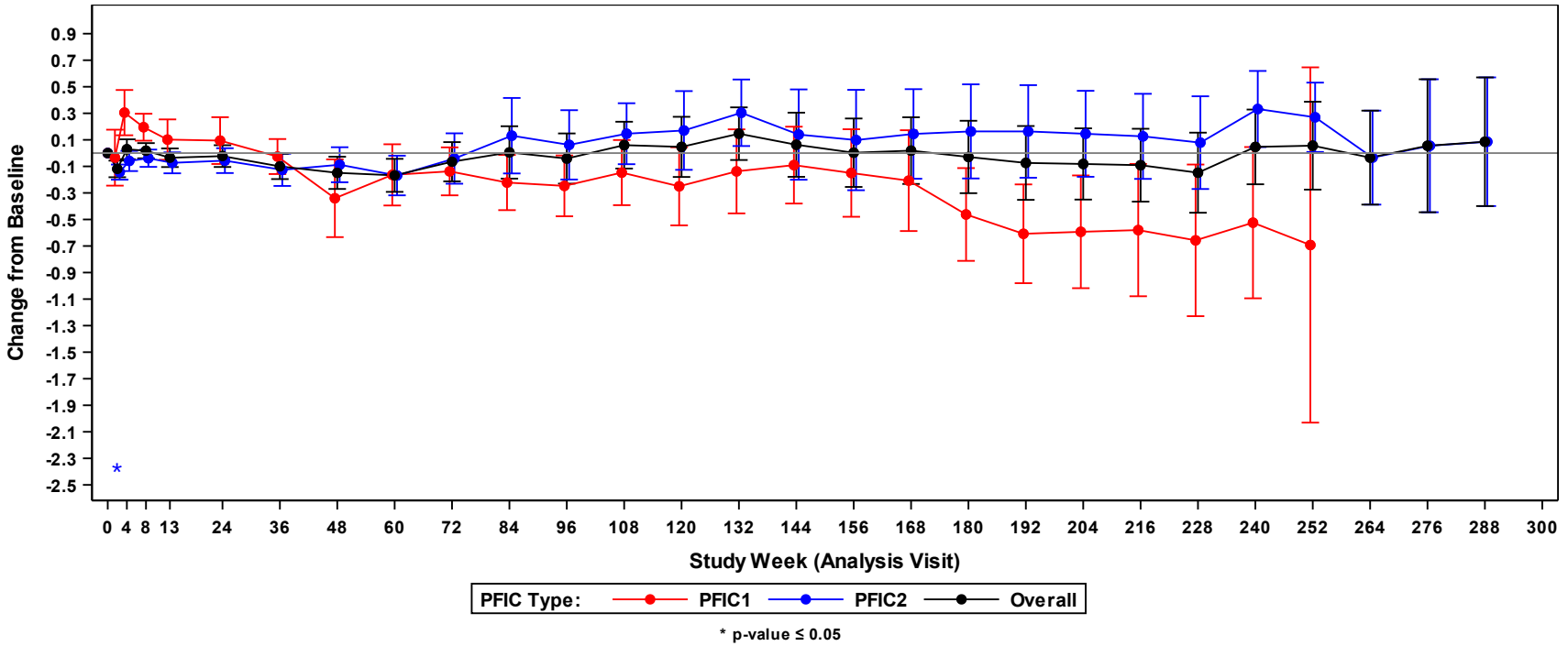
5.1.3.6. Height, Weight, and BMI

There was no change over time in height z-score in the overall and PFIC2 population (Appendix 8.1, Table 14.2.16.1). Although mean CFB in height z-scores were initially positive for participants with PFIC1, values became negative at Week 36, and then showed a further decline after Week 168, indicating a trend toward worsening over time, and an increasing deviation from height compared to healthy age- and gender-matched norms (Figure 5-9).

There was no change over time in weight z-score in the overall and PFIC2 population Appendix 8.1, Table 14.2.16.2). In participants with PFIC1, mean CFB in weight z-scores were positive, indicating a trend toward improved weight gain compared to healthy peers, from Week 72 onwards, at all analysis visits where data were available (Figure 5-10).

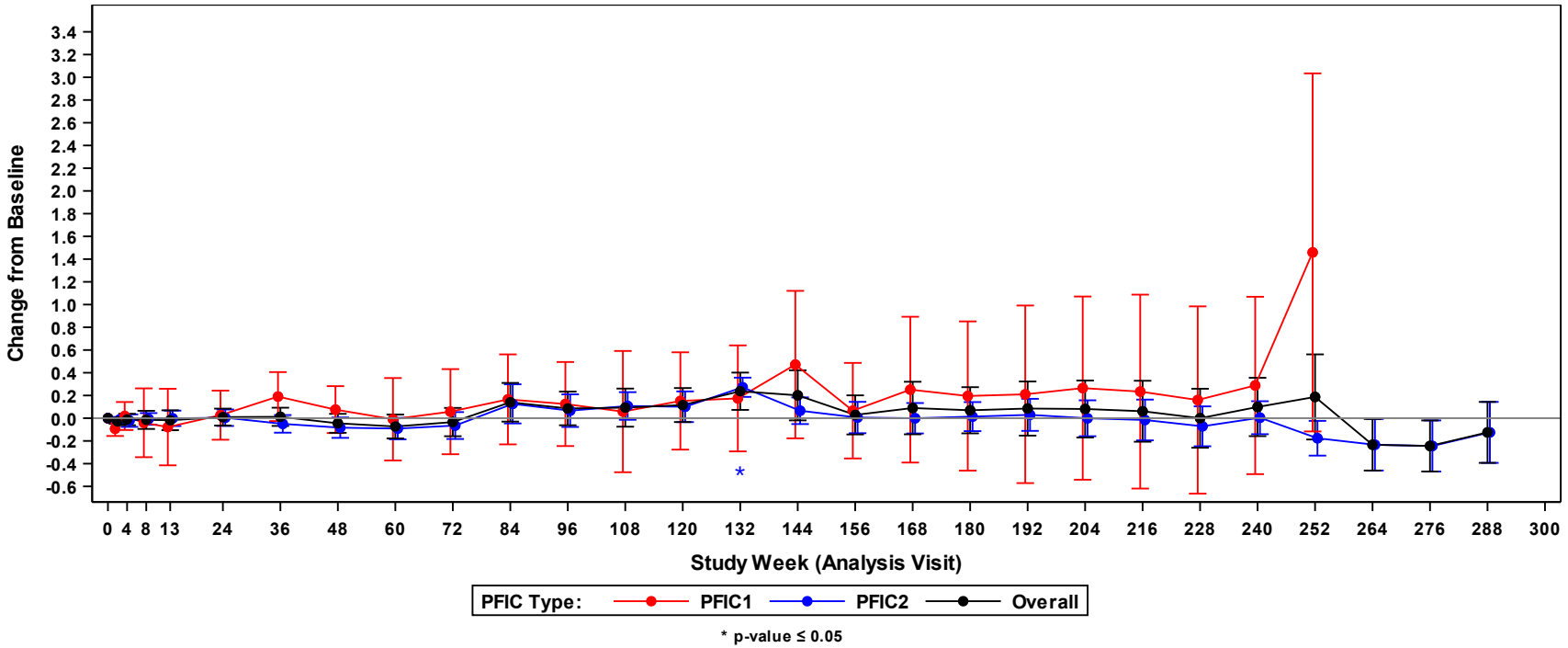
Changes from baseline in BMI z-scores are shown in Appendix 8.1, Table 14.2.16.3. Height, weight, and BMI z-scores are provided for each participant in Appendix 8.2, Listing 16.7.6.

Figure 5-9: Mean (SE) Change From Baseline in Height z-Score by PFIC Type Over Time (Intent-to-Treat Population)



Source: Appendix 8.1, Figure 14.2.16.1
Abbreviations: CFB = change from baseline; PFIC = progressive familial intrahepatic cholestasis; SE = standard error of the mean
Note: Baseline was defined as the last observation obtained before the first dose. Only analysis visits with an overall n ≥ 4 were summarized. Participants that did not complete at least 1 post-Week 72 assessment were excluded from all post-Week 72 analyses. Participants that did not complete at least 1 post-Week 124 assessment were excluded from all post-Week 124 analyses. * Paired t-test used to test if mean change is statistically significant (null hypothesis is that the mean CFB is equal to zero).

Figure 5-10: Mean (SE) Change From Baseline in Weight z-Score by PFIC Type Over Time (Intent-to-Treat Population)



Source: Appendix 8.1, Figure 14.2.16.2
Abbreviations: CFB = change from baseline; PFIC = progressive familial intrahepatic cholestasis; SE = standard error of the mean
Note: Baseline was defined as the last observation obtained before the first dose. Only analysis visits with an overall n ≥4 were summarized. Participants that did not complete at least 1 post-Week 72 assessment were excluded from all post-Week 72 analyses. Participants that did not complete at least 1 post-Week 124 assessment were excluded from all post-Week 124 analyses. * Paired t-test used to test if mean change is statistically significant (null hypothesis is that the mean CFB is equal to zero).

5.1.3.7. Additional Exploratory Efficacy Variables

Additional exploratory efficacy variables are presented in participant listings (Table 5-3).

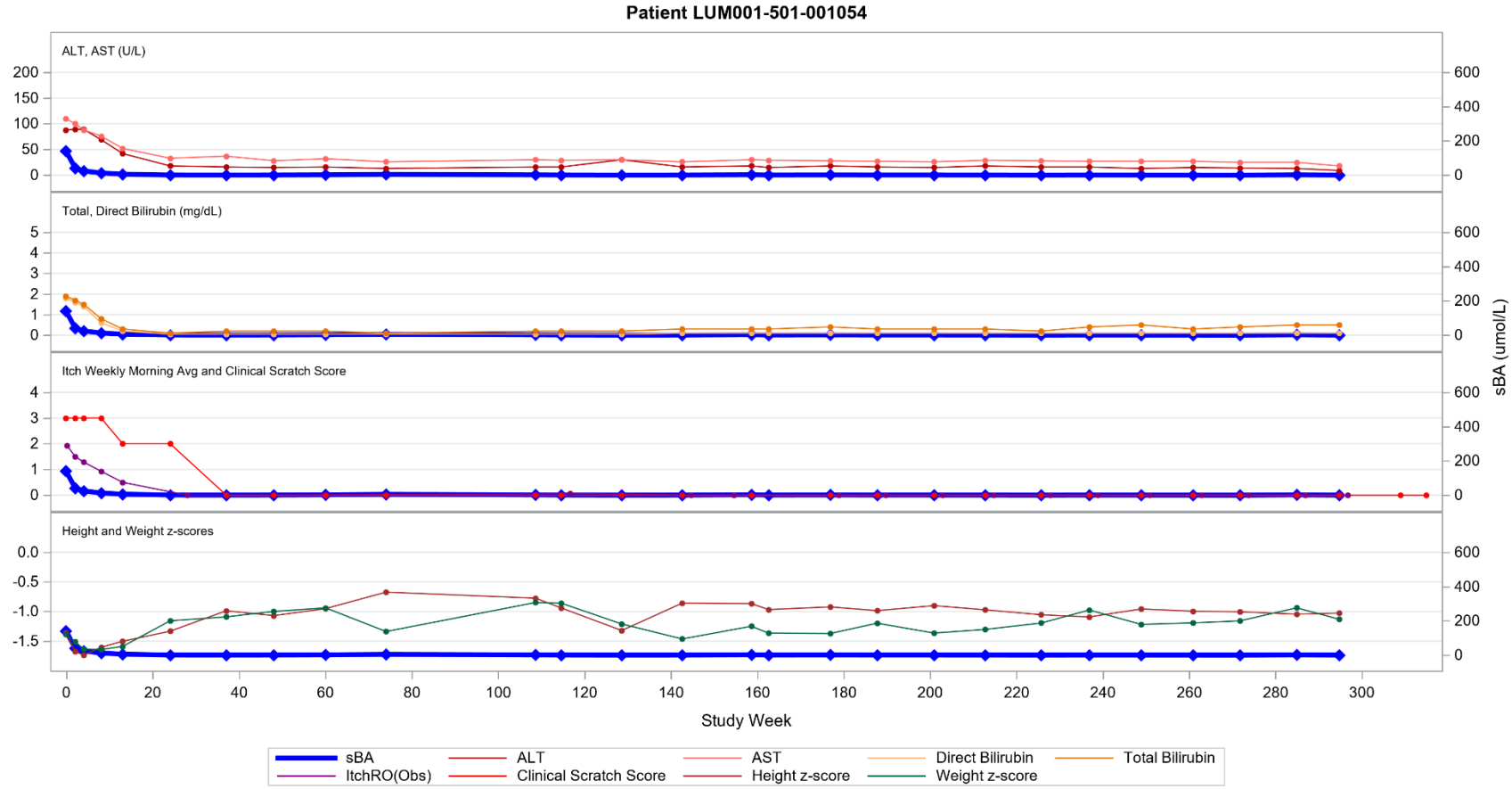
Table 5-3: Exploratory Efficacy Variables Presented in Participant Listings

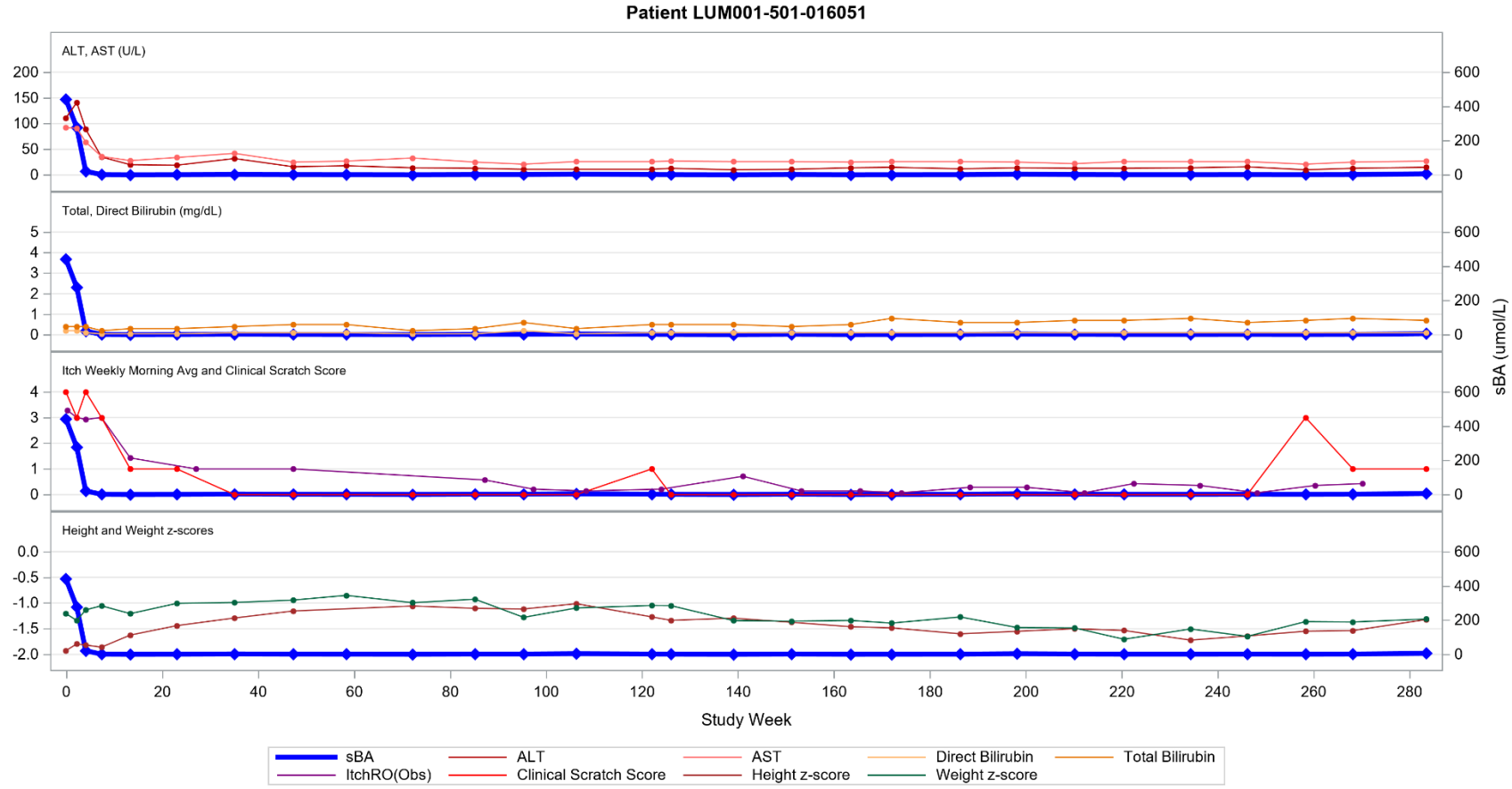
Variable	Listing Number
Patient impression of change	16.1.1, 16.7.4
Caregiver impression of change	16.1.1, 16.7.4
Caregiver global therapeutic benefit	16.7.4
Autotaxin	16.1.1, 16.7.5, 16.10.6
Activated partial thromboplastin time	16.7.5
Prothrombin time	16.7.5
International normalized ratio	16.1.1, 16.7.5
Triglycerides	16.7.5, 16.10.5
High-density lipoprotein cholesterol	16.7.5, 16.10.5
Fibroblast growth factor 19	16.1.1, 16.7.5, 16.10.6
Fibroblast growth factor 21	16.7.5, 16.10.6
Serum bile acid sub-species (taurocholic acid, taurochenodeoxycholic acid, tauroursodeoxycholic acid, taurodeoxycholic acid, taurolithocholic acid, glycocholic acid, glycoursodeoxycholic acid, glycochenodeoxycholic acid, glycodeoxycholic acid, glycolithocholic acid, cholic acid, ursodeoxycholic acid, chenodeoxycholic acid, deoxycholic acid, and lithocholic acid) and the ratio of cholic acid and chenodeoxycholic acid	16.1.2, 16.10.6

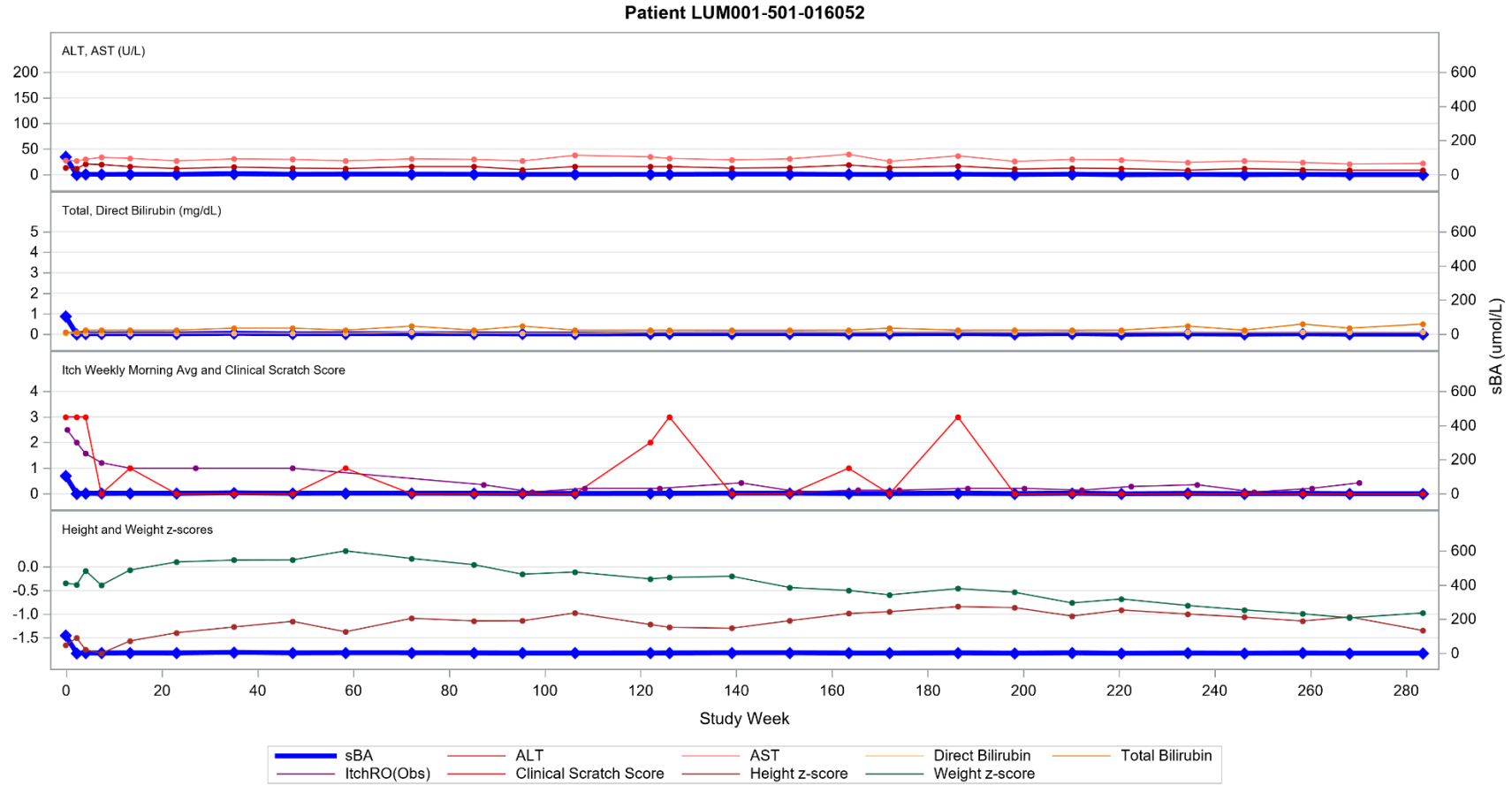
5.1.4. Posthoc Analyses

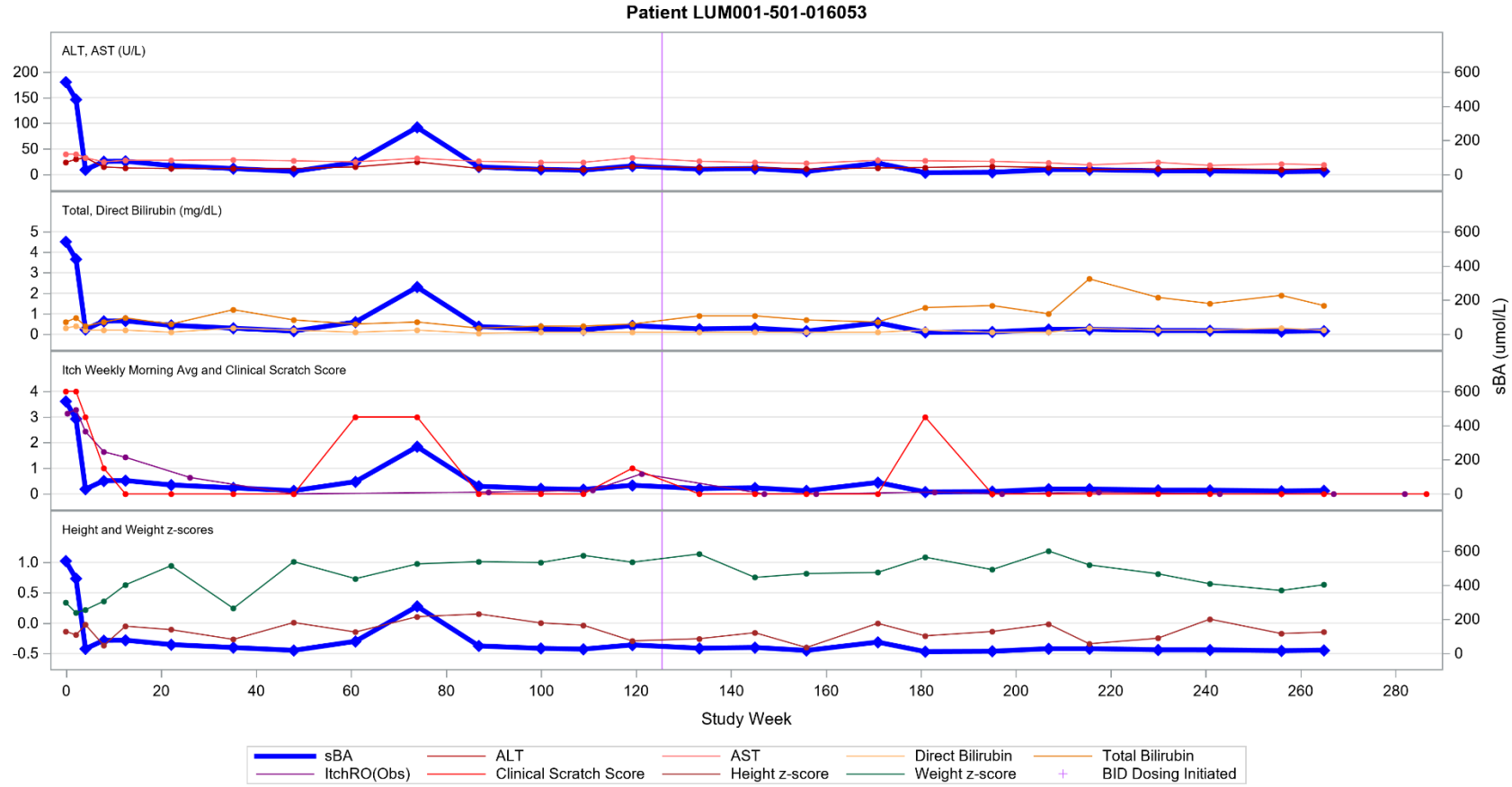
A subset of 7 participants demonstrated a profound and sustained multi-parameter response to maralixibat treatment (Figure 5-11). All of these treatment responders had a non-truncating PFIC2 mutation (i.e., mutation leading to various degrees of residual BSEP activity and a mild-to-moderate clinical presentation). They all experienced a profound and sustained response pattern on multiple clinically relevant parameters including control of sBA (defined as ≥75% reduction of sBA levels from baseline or sBA levels < 102 µmol/L), combined with ≥1.0 reduction in ItchRO(Obs), a normalization of liver transaminases and bilirubin levels (if elevated at baseline), and a statistically significant improvement in growth, as measured by a positive height and weight z-score CFB. Of these 7 treatment responders, all had elevated sBA above 3 times ULN at baseline, with 6 having sBA baseline levels between 104-541 µmol/L. At the 280 µg/kg/day dose, 6 of the 7 responders achieved the sBA response defined above. One further participant (Participant 016054) achieved sBA response after introduction of BID dosing (280 µg/kg BID). All 7 participants who demonstrated this response to maralixibat treatment remained on the study for over 5 years.

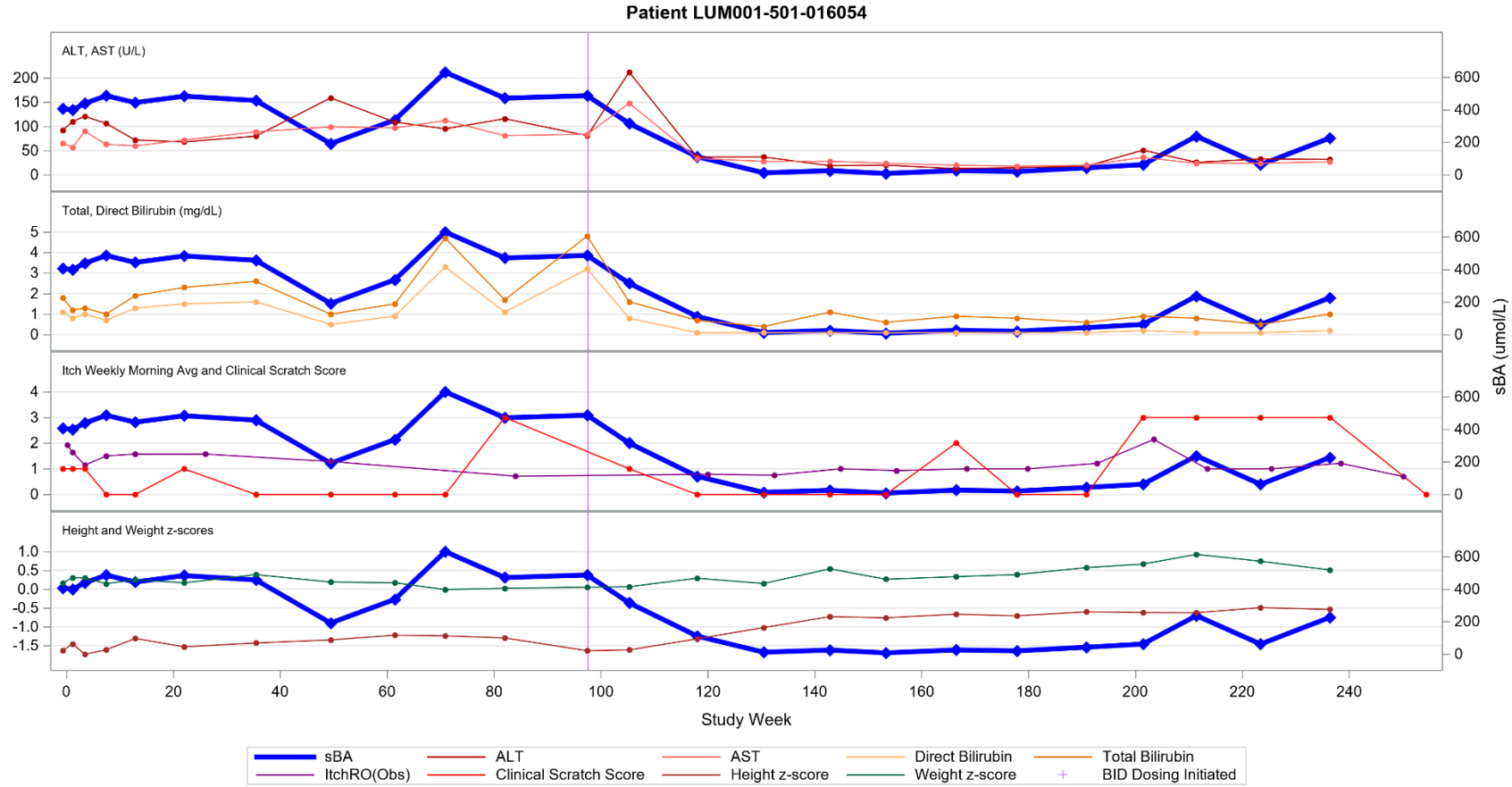
Figure 5-11: Maralixibat Treatment Responders (Intent-to-Treat Population)

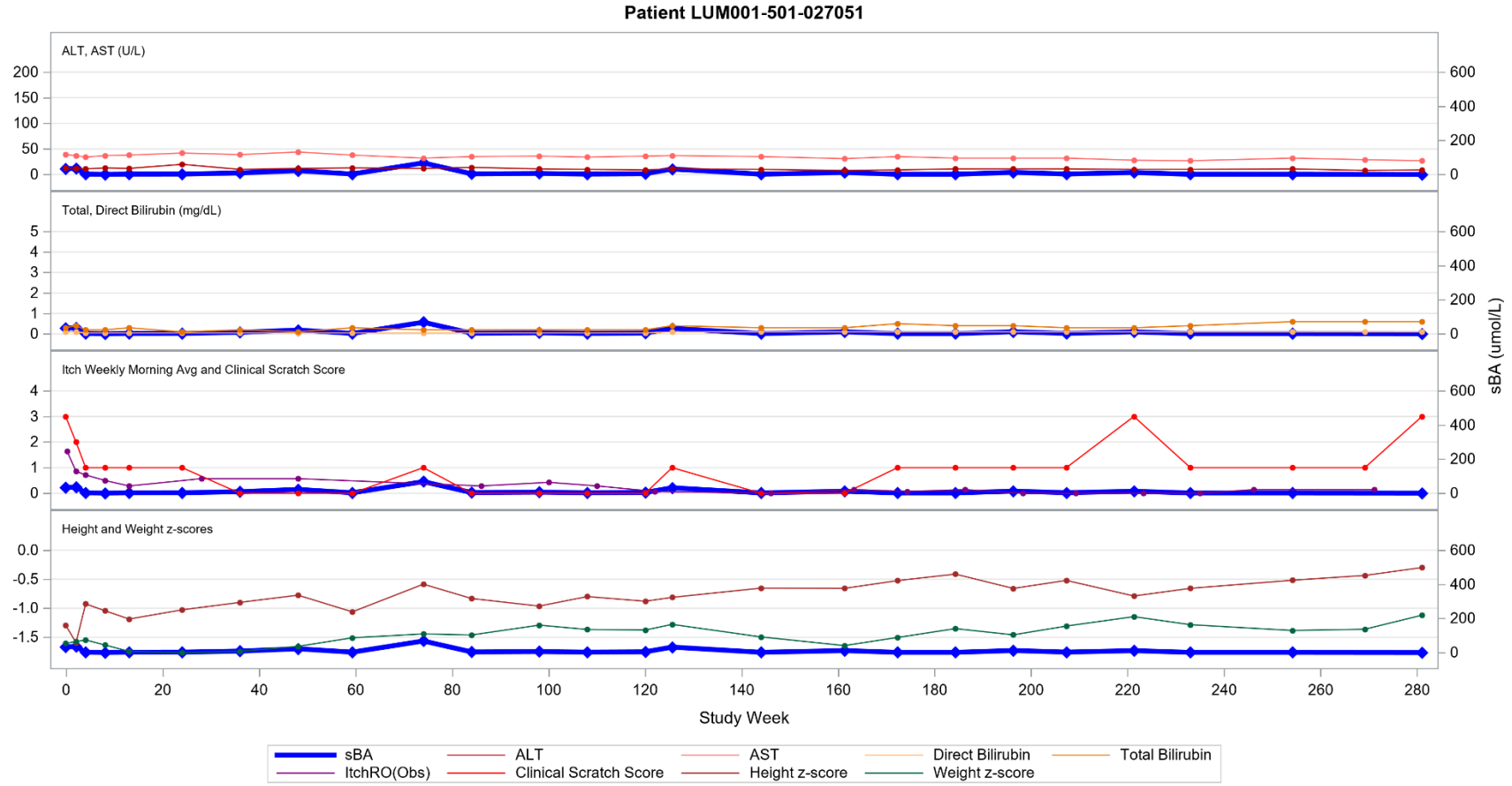


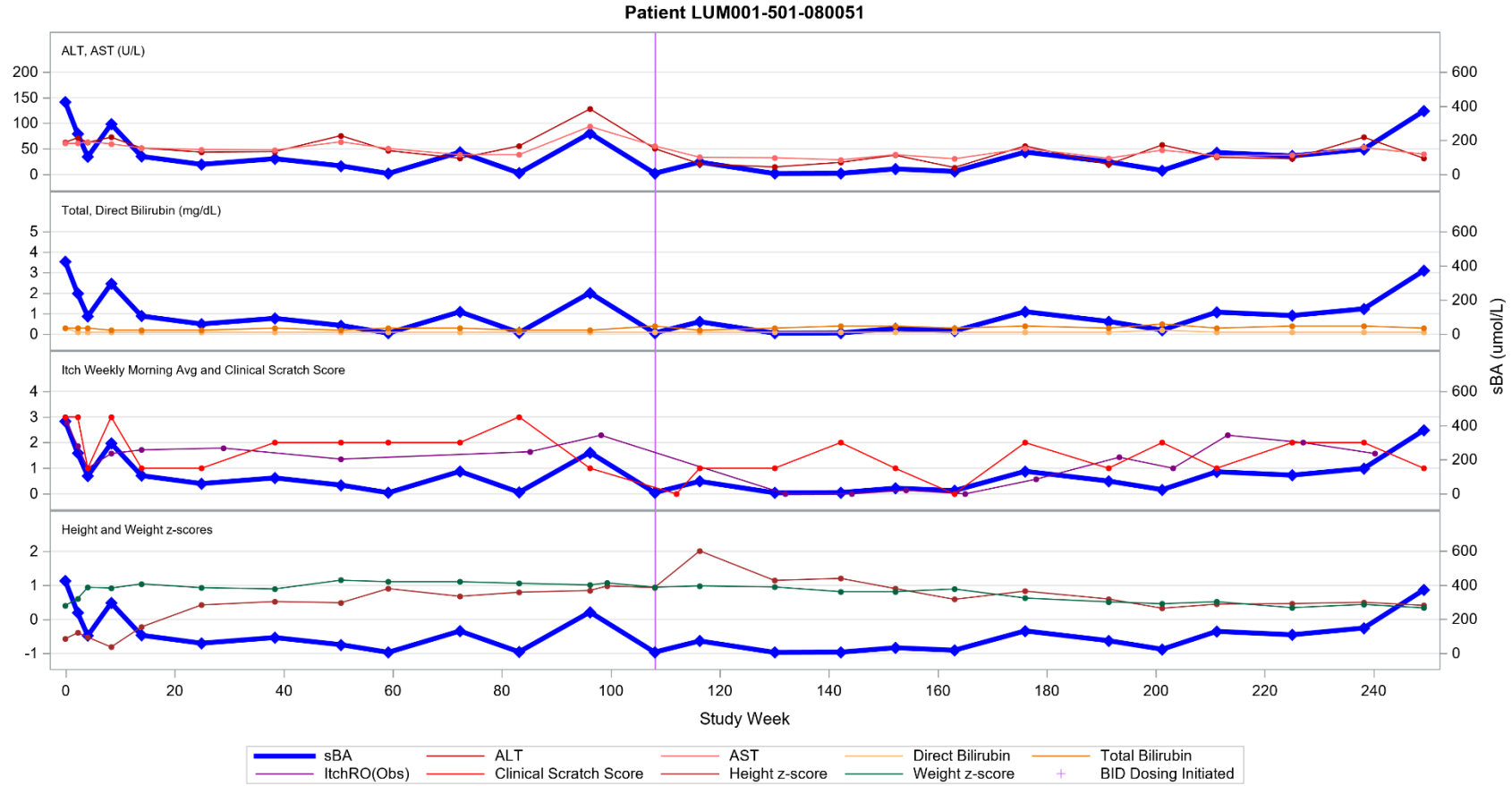

Patient LUM001-501-016051
ALT, AST (U/L)
Total, Direct Bilirubin (mg/dL)
Itch Weekly Morning Avg and Clinical Scratch Score
Height and Weight z-scores
sBA (umol/L)
Study Week
sBA
ItchRO(Obs)
ALT
Clinical Scratch Score
AST
Height z-score
Direct Bilirubin
Weight z-score
Total Bilirubin


Patient LUM001-501-016052
ALT, AST (U/L)
Total, Direct Bilirubin (mg/dL)
Itch Weekly Morning Avg and Clinical Scratch Score
Height and Weight z-scores
sBA (umol/L)
Study Week
sBA
ItchRO(Obs)
ALT
Clinical Scratch Score
AST
Height z-score
Direct Bilirubin
Weight z-score
Total Bilirubin


Patient LUM001-501-016053
ALT, AST (U/L)
Total, Direct Bilirubin (mg/dL)
Itch Weekly Morning Avg and Clinical Scratch Score
Height and Weight z-scores
sBA (umol/L)
Study Week
sBA
ItchRO(Obs)
ALT
Clinical Scratch Score
AST
Height z-score
Direct Bilirubin
Weight z-score
Total Bilirubin
BID Dosing Initiated


Patient LUM001-501-016054
ALT, AST (U/L)
Total, Direct Bilirubin (mg/dL)
Itch Weekly Morning Avg and Clinical Scratch Score
Height and Weight z-scores
sBA (umol/L)
Study Week
sBA
ItchRO(Obs)
ALT
Clinical Scratch Score
AST
Height z-score
Direct Bilirubin
Weight z-score
Total Bilirubin
BID Dosing Initiated


Patient LUM001-501-027051
ALT, AST (U/L)
Total, Direct Bilirubin (mg/dL)
Itch Weekly Morning Avg and Clinical Scratch Score
Height and Weight z-scores
sBA (umol/L)
Study Week
sBA
ItchRO(Obs)
ALT
Clinical Scratch Score
AST
Height z-score
Direct Bilirubin
Weight z-score
Total Bilirubin



Source: Figure provided by Mirum Pharmaceuticals, Inc., using data from Appendix 8.2, Listing 16.7.2, 16.7.3.1, 16.7.5, and 16.7.6.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; Avg =average; BID = twice daily; ItchRO(Obs) = Itch Reported Outcome (Observer); sBA = serum bile acid

5.2. Safety

5.2.1. Adverse Events

5.2.1.1. Brief Summary of Adverse Events

Table 5-4 presents an overview of the occurrence of TEAEs in the Safety Population during the study; the pattern of which is broadly consistent with that presented in the LUM001-501 Final CSR for TEAEs observed during the first 72 weeks. No deaths were reported during the conduct of the study. All participants had at least 1 TEAE. Treatment-emergent AEs potentially related to study drug were experienced by 26 participants (78.8%) overall (an increase of 3 participants from the first 72 weeks of treatment), with a lower incidence in participants with PFIC1 (6 participants [75.0%]) compared to participants with PFIC2 (20 participants [80.0%]). Serious TEAEs were experienced by 15 participants (45.5%) overall (an increase of 1 participant from the first 72 weeks of treatment), including 4 participants (50.0%) with PFIC1 and 11 participants (44.0%) with PFIC2. Serious TEAEs potentially related to study drug were experienced by 5 participants (15.2%) overall (no increase from the first 72 weeks of treatment), 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 10 participants (30.3%) overall; with a lower incidence in participants with PFIC1 (1 participant [12.5%]) compared to participants with PFIC2 (9 participants [36.0%]). The frequency of TEAEs leading to study drug discontinuation during the study doubled the number reported in the first 72 weeks in the LUM001-501 Final CSR; 1 participant with PFIC1 and an additional 4 participants with PFIC2 experienced TEAEs leading to study drug discontinuation after 72 weeks of treatment with MRX. The final analysis also included a breakdown of TEAEs by MRX dose. However, few participants had their dose escalated to 280 µg/kg BID, so interpretation of results should be cautious; in subsequent tables TEAEs are presented by MRX dose, but generally not discussed in the text.

Table 5-4: Summary of Treatment-emergent Adverse Events by PFIC Type and MRX Dose (Safety Population)

Category	280 µg/kg QD n (%)	280 µg/kg BID n (%)	Any Dose n (%)
PFIC Type: Overall	**N=33**	**N=10**	**N=33**
Participants with at Least 1:			
TEAE	33 (100.0)	10 (100.0)	33 (100.0)
TEAE Potentially Related to Study Drug[a]	24 (72.7)	5 (50.0)	26 (78.8)
Serious TEAE	15 (45.5)	0	15 (45.5)
Serious TEAE Potentially Related to Study Drug[a]	5 (15.2)	0	5 (15.2)
TEAE Leading to Study Drug Discontinuation	9 (27.3)	1 (10.0)	10 (30.3)
TEAE Leading to Death	0	0	0

Category	280 µg/kg QD n (%)	280 µg/kg BID n (%)	Any Dose n (%)
PFIC Type: PFIC1	**N=8**	**N=5**	**N=8**
Participants with at Least 1			
TEAE	8 (100.0)	5 (100.0)	8 (100.0)
TEAE Potentially Related to Study Drug[a]	4 (50.0)	3 (60.0)	6 (75.0)
Serious TEAE	4 (50.0)	0	4 (50.0)
Serious TEAE Potentially Related to Study Drug[a]	1 (12.5)	0	1 (12.5)
TEAE Leading to Study Drug Discontinuation	0	1 (20.0)	1 (12.5)
TEAE Leading to Death	0	0	0
PFIC Type: PFIC2	**N=25**	**N=5**	**N=25**
Participants with at Least 1			
TEAE	25 (100.0)	5 (100.0)	25 (100.0)
TEAE Potentially Related to Study Drug[a]	20 (80.0)	2 (40.0)	20 (80.0)
Serious TEAE	11 (44.0)	0	11 (44.0)
Serious TEAE Potentially Related to Study Drug[a]	4 (16.0)	0	4 (16.0)
TEAE Leading to Study Drug Discontinuation	9 (36.0)	0	9 (36.0)
TEAE Leading to Death	0	0	0

Source: Appendix 8.1, Table 14.3.2.1

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

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

Note: Percentages are 100*n/N. The 280 QD dose included all QD doses ≤280 µg/kg. The 280 BID dose included the dose of 420 µg/kg daily for 2 weeks as part of a dose-escalation. For each MRX dose group, the percent of participants was derived using a denominator based on the number of participants that received the given dose. In presenting AEs by MRX dose, events were only counted in the MRX dose group in which the start of the event occurred. Participants were counted only once for each System Organ Class and Preferred Term. Treatment-emergent adverse events are AEs with a start date on or after the first dose of study drug and started prior to the last dose of study drug plus 14 days. 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 5-5 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 gastrointestinal disorders SOC, respiratory, thoracic and mediastinal disorders SOC, and general disorders and administration site conditions SOC. Preferred terms reported most often included the following: pyrexia (20 participants [60.6%]), diarrhea (19 participants [57.6%]), cough (18 participants [54.5%]), and vomiting (17 participants [51.5%]). The most frequently reported PTs for the

duration of the study were the same as those presented for the first 72 weeks of treatment in the LUM001-501 Final CSR. Preferred terms reported in 3 or more participants for the first time after Week 72 were: nausea, jaundice, seasonal allergy, varicella, conjunctivitis, ear infection, influenza, gastroenteritis viral, rhinitis, tooth abscess, urinary tract infection, procedural pain, alanine aminotransferase increased, aspartate aminotransferase increased, hypocalcaemia, headache, rhinorrhea, and nasal congestion.

Table 5-5: Incidence of Treatment-emergent Adverse Events in 3 or More Participants During the Study (Safety Population)

System Organ Class[a] Preferred Term	280 µg/kg QD (N=33) n (%)	280 µg/kg BID (N=10) n (%)	Any Dose (N=33) n (%)
Number of Participants with at Least 1 TEAE	33 (100.0)	10 (100.0)	33 (100.0)
Ear and labyrinth disorders	5 (15.2)	3 (30.0)	6 (18.2)
Ear pain	3 (9.1)	3 (30.0)	5 (15.2)
Gastrointestinal disorders	28 (84.8)	7 (70.0)	28 (84.8)
Diarrhoea	18 (54.5)	4 (40.0)	19 (57.6)
Vomiting	16 (48.5)	5 (50.0)	17 (51.5)
Abdominal pain	14 (42.4)	3 (30.0)	15 (45.5)
Abdominal pain upper	7 (21.2)	3 (30.0)	8 (24.2)
Faeces pale	5 (15.2)	2 (20.0)	6 (18.2)
Constipation	5 (15.2)	1 (10.0)	5 (15.2)
Frequent bowel movements	4 (12.1)	0	4 (12.1)
Toothache	4 (12.1)	0	4 (12.1)
Nausea	3 (9.1)	0	3 (9.1)
General disorders and administration site conditions	25 (75.8)	8 (80.0)	25 (75.8)
Pyrexia	18 (54.5)	8 (80.0)	20 (60.6)
Fatigue	3 (9.1)	1 (10.0)	4 (12.1)
Influenza like illness	3 (9.1)	0	3 (9.1)
Malaise	3 (9.1)	0	3 (9.1)
Hepatobiliary disorders	10 (30.3)	3 (30.0)	11 (33.3)
Hyperbilirubinaemia	3 (9.1)	2 (20.0)	3 (9.1)
Jaundice	2 (6.1)	1 (10.0)	3 (9.1)
Immune system disorders	1 (3.0)	2 (20.0)	3 (9.1)
Seasonal allergy	1 (3.0)	2 (20.0)	3 (9.1)

System Organ Class[a] Preferred Term	280 µg/kg QD (N=33) n (%)	280 µg/kg BID (N=10) n (%)	Any Dose (N=33) n (%)
Infections and infestations	30 (90.9)	9 (90.0)	30 (90.9)
Nasopharyngitis	13 (39.4)	6 (60.0)	15 (45.5)
Upper respiratory tract infection	8 (24.2)	5 (50.0)	11 (33.3)
Gastroenteritis	5 (15.2)	0	5 (15.2)
Varicella	5 (15.2)	0	5 (15.2)
Conjunctivitis	3 (9.1)	1 (10.0)	4 (12.1)
Ear infection	3 (9.1)	1 (10.0)	4 (12.1)
Influenza	2 (6.1)	2 (20.0)	4 (12.1)
Pharyngitis streptococcal	3 (9.1)	2 (20.0)	4 (12.1)
Viral infection	3 (9.1)	1 (10.0)	4 (12.1)
Gastroenteritis viral	2 (6.1)	1 (10.0)	3 (9.1)
Rhinitis	2 (6.1)	1 (10.0)	3 (9.1)
Tooth abscess	2 (6.1)	1 (10.0)	3 (9.1)
Urinary tract infection	3 (9.1)	1 (10.0)	3 (9.1)
Injury, poisoning and procedural complications	15 (45.5)	3 (30.0)	17 (51.5)
Procedural pain	3 (9.1)	0	3 (9.1)
Traumatic haemorrhage	3 (9.1)	0	3 (9.1)
Investigations	13 (39.4)	4 (40.0)	14 (42.4)
International normalised ratio increased	7 (21.2)	1 (10.0)	7 (21.2)
Blood bilirubin increased	6 (18.2)	0	6 (18.2)
Alanine aminotransferase increased	2 (6.1)	1 (10.0)	3 (9.1)
Aspartate aminotransferase increased	2 (6.1)	1 (10.0)	3 (9.1)
Metabolism and nutrition disorders	12 (36.4)	2 (20.0)	13 (39.4)
Vitamin D deficiency	4 (12.1)	0	4 (12.1)
Decreased appetite	3 (9.1)	0	3 (9.1)
Hypocalcaemia	3 (9.1)	0	3 (9.1)
Musculoskeletal and connective tissue disorders	10 (30.3)	1 (10.0)	11 (33.3)
Pain in extremity	6 (18.2)	0	6 (18.2)
Nervous system disorders	9 (27.3)	2 (20.0)	10 (30.3)
Headache	6 (18.2)	2 (20.0)	7 (21.2)

System Organ Class[a] Preferred Term	280 µg/kg QD (N=33) n (%)	280 µg/kg BID (N=10) n (%)	Any Dose (N=33) n (%)
Psychiatric disorders	11 (33.3)	1 (10.0)	11 (33.3)
Irritability	5 (15.2)	1 (10.0)	5 (15.2)
Respiratory, thoracic and mediastinal disorders	25 (75.8)	8 (80.0)	26 (78.8)
Cough	17 (51.5)	6 (60.0)	18 (54.5)
Oropharyngeal pain	9 (27.3)	6 (60.0)	13 (39.4)
Epistaxis	9 (27.3)	0	9 (27.3)
Rhinorrhoea	5 (15.2)	5 (50.0)	8 (24.2)
Nasal congestion	3 (9.1)	1 (10.0)	4 (12.1)
Skin and subcutaneous tissue disorders	16 (48.5)	3 (30.0)	18 (54.5)
Pruritus	9 (27.3)	2 (20.0)	11 (33.3)
Rash	5 (15.2)	1 (10.0)	5 (15.2)

Source: Appendix 8.1, Table 14.3.2.2
Abbreviations: AE = adverse event; BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; n = number in a given category; N = number of participants; QD = once daily; TEAE = treatment-emergent adverse event
a Adverse events were coded using MedDRA version 22.1.
Note: Percentages are 100*n/N. The 280 QD dose included all QD doses ≤280 µg/kg. The 280 BID dose included the dose of 420 µg/kg daily for 2 weeks as part of a dose-escalation. For each MRX dose group, the percent of participants was derived using a denominator based on the number of participants that received the given dose. In presenting AEs by MRX dose, events were only counted in the MRX dose group in which the start of the event occurred. Participants were counted only once for each System Organ Class and Preferred Term. Treatment-emergent adverse events are AEs with a start date on or after the first dose of study drug and started prior to the last dose of study drug plus 14 days. 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 CTCAE Grade 5 (fatal) severity were reported. Fourteen participants experienced a CTCAE Grade 3 or CTCAE Grade 4 TEAE during the study; an increase of 1 participant since Week 72, as reported in the LUM001-501 Final CSR. Two participants experienced CTCAE Grade 4 TEAEs during the study: 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 5-6 provides a summary of TEAEs that were considered at least CTCAE Grade 3. A total of 12 participants (36.4%), an increase of 1 participant since Week 72, experienced TEAEs of maximum severity Grade 3 during the study. The severe (Grade 3) TEAEs included the following: blood bilirubin increased (4 participants [12.1%]); diarrhea, disease progression, and pruritus (2 participants [6.1%]) each; abdominal pain, diarrhea

hemorrhagic, pancreatic failure, pancreatitis, hyperbilirubinemia, upper limb fracture, ALT increased, bilirubin conjugated increased, iron deficiency, malnutrition, encephalopathy, seizure, irritability, and sleep apnea syndrome (1 participant [3.0%] each).

Table 5-6: Incidence of CTCAE Grade 3 and 4 Treatment-emergent Adverse Events by Maximum Severity and MRX Dose (Safety Population)

System Organ Class[a] Preferred Term[b]	CTCAE Grade	280 µg/kg QD (N=33) n (%)	280 µg/kg BID (N=10) n (%)	Any Dose (N=33) n (%)
Gastrointestinal disorders				
Diarrhoea	3	2 (6.1)	0	2 (6.1)
Abdominal pain	3	1 (3.0)	0	1 (3.0)
Diarrhoea haemorrhagic	3	1 (3.0)	0	1 (3.0)
Pancreatic failure	3	1 (3.0)	0	1 (3.0)
Pancreatitis	3	1 (3.0)	0	1 (3.0)
General disorders and administration site conditions				
Disease progression	3	2 (6.1)	0	2 (6.1)
Hepatobiliary disorders				
Hyperbilirubinaemia	3	1 (3.0)	1 (10.0)	1 (3.0)
Hyperbilirubinaemia	4	1 (3.0)	0	1 (3.0)
Injury, poisoning and procedural complications				
Upper limb fracture	3	1 (3.0)	0	1 (3.0)
Investigations				
Blood bilirubin increased	3	4 (12.1)	0	4 (12.1)
Alanine aminotransferase increased	3	0	1 (10.0)	1 (3.0)
Alanine aminotransferase increased	4	1 (3.0)	0	1 (3.0)
Aspartate aminotransferase increased	4	1 (3.0)	0	1 (3.0)
Bilirubin conjugated increased	3	1 (3.0)	0	1 (3.0)
Metabolism and nutrition disorders				
Iron deficiency	3	1 (3.0)	0	1 (3.0)
Malnutrition	3	1 (3.0)	0	1 (3.0)
Nervous system disorders				
Encephalopathy	3	1 (3.0)	0	1 (3.0)
Seizure	3	1 (3.0)	0	1 (3.0)

System Organ Class[a] Preferred Term[b]	CTCAE Grade	280 µg/kg QD (N=33) n (%)	280 µg/kg BID (N=10) n (%)	Any Dose (N=33) n (%)
Psychiatric disorders				
Irritability	3	1 (3.0)	0	1 (3.0)
Respiratory, thoracic and mediastinal disorders				
Sleep apnoea syndrome	3	0	1 (10.0)	1 (3.0)
Skin and subcutaneous tissue disorders				
Pruritus	3	2 (6.1)	0	2 (6.1)

Source: Appendix 8.1, Table 14.3.2.3
Abbreviations: AE = adverse event; BID = twice daily; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; n = number in a given category; N = number of participants; QD = once daily; TEAE = treatment-emergent adverse event
a Adverse events were coded using MedDRA version 22.1.
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. The 280 QD dose included all QD doses ≤280 µg/kg. The 280 BID dose included the dose of 420 µg/kg daily for 2 weeks as part of a dose-escalation. For each MRX dose group, the percent of participants was derived using a denominator based on the number of participants that received the given dose. In presenting AEs by MRX dose, events were only counted in the MRX dose group in which the start of the event occurred. Participants were counted only once for each System Organ Class and Preferred Term. Treatment-emergent adverse events are AEs with a start date on or after the first dose of study drug and started prior to the last dose of study drug plus 14 days. 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 5-7 displays TEAEs judged to be potentially related to study treatment that were reported in 2 or more participants during the study. Treatment-related TEAEs were experienced by 26 participants (78.8%) during the study, an increase of 3 participants since Week 72, as reported in the LUM001-501 Final CSR. The most common treatment-related TEAEs included diarrhea (13 participants [39.4%]), abdominal pain (9 participants [27.3%]), abdominal pain upper (6 participants [18.2%]), vomiting (5 participants [15.2%]), and INR increased (5 participants [15.2%]). The distribution of PTs was consistent with those reported up to Week 72; no new PTs were reported for treatment-related TEAEs after Week 72.

Table 5-7: Incidence of Treatment-related Treatment-emergent Adverse Events in 2 or More Participants During the Study (Safety Population)

System Organ Class[a] Preferred Term	280 µg/kg QD (N=33) n (%)	280 µg/kg BID (N=10) n (%)	Any Dose (N=33) n (%)
Number of Participants with at Least 1 Treatment-related TEAE	24 (72.7)	5 (50.0)	26 (78.8)
Gastrointestinal disorders			
Diarrhoea	11 (33.3)	2 (20.0)	13 (39.4)
Abdominal pain	8 (24.2)	1 (10.0)	9 (27.3)
Abdominal pain upper	6 (18.2)	0	6 (18.2)
Vomiting	5 (15.2)	0	5 (15.2)
Frequent bowel movements	4 (12.1)	0	4 (12.1)
Faeces pale	2 (6.1)	0	2 (6.1)
Hepatobiliary disorders			
Hyperbilirubinaemia	2 (6.1)	1 (10.0)	2 (6.1)
Investigations			
International normalised ratio increased	5 (15.2)	1 (10.0)	5 (15.2)
International normalised ratio abnormal	2 (6.1)	0	2 (6.1)
Vitamin E decreased	2 (6.1)	0	2 (6.1)
Metabolism and nutrition disorders			
Decreased appetite	2 (6.1)	0	2 (6.1)
Vitamin D deficiency	2 (6.1)	0	2 (6.1)
Psychiatric disorders			
Irritability	2 (6.1)	0	2 (6.1)
Skin and subcutaneous tissue disorders			
Pruritus	2 (6.1)	1 (10.0)	3 (9.1)

Source: Appendix 8.1, Table 14.3.2.4

Abbreviations: AE = adverse event; BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; n = number in a given category; N = number of participants; QD = once daily; TEAE = treatment-emergent adverse event

a Adverse events were coded using MedDRA version 22.1.

Note: Percentages are 100*n/N. The 280 QD dose included all QD doses ≤280 µg/kg. The 280 BID dose included the dose of 420 µg/kg daily for 2 weeks as part of a dose-escalation. For each MRX dose group, the percent of participants was derived using a denominator based on the number of participants that received the given dose. In presenting AEs by MRX dose, events were only counted in the MRX dose group in which the start of the event occurred. Participants were counted only once for each System Organ Class and Preferred Term. Treatment-emergent adverse events are AEs with a start date on or after the first dose of study drug and started prior to the last dose of study drug plus 14 days. 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 14.3.2.10).

5.2.1.4. Serious Adverse Events

Narratives for participants who had a treatment-emergent SAE during the study are provided in Appendix 10.

Table 5-8 provides a summary of SAEs during the study. Serious AEs were experienced by 15 participants (45.5%) during the study, with 1 additional participant experiencing an SAE (vomiting) after Week 72. Gastrointestinal events were the most frequently reported SAEs (7 participants [21.2%]). The only SAEs reported for more than 1 participant were abdominal pain, diarrhea, and gastroenteritis, each experienced by 2 participants (6.1%). No SAEs were experienced by participants on a dose of MRX of 280 µg/kg BID.

Table 5-8: Incidence of Treatment-emergent Serious Adverse Events During the Study (Safety Population)

System Organ Class[a] Preferred Term	280 µg/kg QD (N=33) n (%)	280 µg/kg BID (N=10) n (%)	Any Dose (N=33) n (%)
Number of Participants with at Least 1 Serious TEAE	15 (45.5)	0	15 (45.5)
Gastrointestinal disorders	7 (21.2)	0	7 (21.2)
Abdominal pain	2 (6.1)	0	2 (6.1)
Diarrhoea	2 (6.1)	0	2 (6.1)
Abdominal pain upper	1 (3.0)	0	1 (3.0)
Melaena	1 (3.0)	0	1 (3.0)
Pancreatitis	1 (3.0)	0	1 (3.0)
Vomiting	1 (3.0)	0	1 (3.0)
General disorders and administration site conditions	1 (3.0)	0	1 (3.0)
Condition aggravated	1 (3.0)	0	1 (3.0)
Hepatobiliary disorders	1 (3.0)	0	1 (3.0)
Cholelithiasis	1 (3.0)	0	1 (3.0)
Infections and infestations	5 (15.2)	0	5 (15.2)
Gastroenteritis	2 (6.1)	0	2 (6.1)
Pneumonia	1 (3.0)	0	1 (3.0)
Respiratory tract infection	1 (3.0)	0	1 (3.0)
Viral infection	1 (3.0)	0	1 (3.0)

System Organ Class[a] Preferred Term	280 µg/kg QD (N=33) n (%)	280 µg/kg BID (N=10) n (%)	Any Dose (N=33) n (%)
Injury, poisoning and procedural complications	2 (6.1)	0	2 (6.1)
Radius fracture	1 (3.0)	0	1 (3.0)
Ulna fracture	1 (3.0)	0	1 (3.0)
Upper limb fracture	1 (3.0)	0	1 (3.0)
Investigations	2 (6.1)	0	2 (6.1)
Blood bilirubin increased	1 (3.0)	0	1 (3.0)
International normalised ratio increased	1 (3.0)	0	1 (3.0)
Metabolism and nutrition disorders	2 (6.1)	0	2 (6.1)
Electrolyte imbalance	1 (3.0)	0	1 (3.0)
Hypocalcaemia	1 (3.0)	0	1 (3.0)
Hypoglycaemia	1 (3.0)	0	1 (3.0)
Respiratory, thoracic and mediastinal disorders	2 (6.1)	0	2 (6.1)
Dyspnoea	1 (3.0)	0	1 (3.0)
Epistaxis	1 (3.0)	0	1 (3.0)
Skin and subcutaneous tissue disorders	1 (3.0)	0	1 (3.0)
Pruritus	1 (3.0)	0	1 (3.0)
Surgical and medical procedures	1 (3.0)	0	1 (3.0)
Enteral nutrition	1 (3.0)	0	1 (3.0)
Gastrointestinal tube insertion	1 (3.0)	0	1 (3.0)

Source: Appendix 8.1, Table 14.3.2.6

Abbreviations: AE = adverse event; BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; n = number in a given category; N = number of participants; QD = once daily; TEAE = treatment-emergent adverse event

a Adverse events were coded using MedDRA version 22.1.

Note: Percentages are 100*n/N. The 280 QD dose included all QD doses ≤280 µg/kg. The 280 BID dose included the dose of 420 µg/kg daily for 2 weeks as part of a dose-escalation. For each MRX dose group, the percent of participants was derived using a denominator based on the number of participants that received the given dose. In presenting AEs by MRX dose, events were only counted in the MRX dose group in which the start of the event occurred. Participants were counted only once for each System Organ Class and Preferred Term. Treatment-emergent adverse events are AEs with a start date on or after the first dose of study drug and started prior to the last dose of study drug plus 14 days. 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 5-9 provides a summary of SAEs reported to be potentially related to study treatment during the study. 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). No new treatment-related SAEs were reported after Week 72.

Table 5-9: Incidence of Treatment-related Treatment-emergent Serious Adverse Events During the Study (Safety Population)

System Organ Class[a] Preferred Term	280 µg/kg QD (N=33) n (%)	280 µg/kg BID (N=10) n (%)	Any Dose (N=33) n (%)
Number of Participants with at Least 1 Treatment-related SAE	5 (15.2)	0	5 (15.2)
Gastrointestinal disorders	3 (9.1)	0	3 (9.1)
Abdominal pain	1 (3.0)	0	1 (3.0)
Abdominal pain upper	1 (3.0)	0	1 (3.0)
Diarrhoea	1 (3.0)	0	1 (3.0)
Pancreatitis	1 (3.0)	0	1 (3.0)
Investigations	2 (6.1)	0	2 (6.1)
Blood bilirubin increased	1 (3.0)	0	1 (3.0)
International normalised ratio increased	1 (3.0)	0	1 (3.0)

Source: Appendix 8.1, Table 14.3.2.7
Abbreviations: AE = adverse event; BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; n = number in a given category; N = number of participants; QD = once daily; SAE = serious adverse event; TEAE = treatment-emergent adverse event
a Adverse events were coded using MedDRA version 22.1.
Note: Percentages are 100*n/N. The 280 QD dose included all QD doses ≤280 µg/kg. The 280 BID dose included the dose of 420 µg/kg daily for 2 weeks as part of a dose-escalation. For each MRX dose group, the percent of participants was derived using a denominator based on the number of participants that received the given dose. In presenting AEs by MRX dose, events were only counted in the MRX dose group in which the start of the event occurred. Participants were counted only once for each System Organ Class and Preferred Term. Treatment-emergent adverse events are AEs with a start date on or after the first dose of study drug and started prior to the last dose of study drug plus 14 days. 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 study are provided in Appendix 10.

Treatment-emergent AEs that resulted in permanent treatment discontinuation during the study are presented in Table 5-10. A total of 10 participants (30.3%) experienced TEAEs that led to permanent treatment discontinuation, 5 of which occurred after Week 72. Three TEAEs (pruritus, pancreatitis, and vitamin E decreased) that led to permanent treatment discontinuation were considered as potentially related to study drug (i.e., determined by the investigator to be possibly related or related) (Appendix 8.2, Listing 16.8.4.1). 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 (4 participants [12.1%]; 2 not related and 2 unlikely/remotely related); hepatic mass (1 participant [3.0%]; not related); vitamin E decreased (1 participant [3.0%]; possibly related); pancreatitis (1 participant [3.0%]; possibly related); and pruritus (1 participant [3.0%]; possibly related). All of the TEAEs that led to permanent treatment discontinuation were experienced by participants with PFIC2, with the exception of 1 participant with PFIC1 (who was also the only participant to have an AE leading to discontinuation while taking a dose of 280 µg/kg BID) that had pruritus (Appendix 8.1, Table 14.3.2.8).

Table 5-10: Incidence of Adverse Events Leading to Permanent Treatment Discontinuation During the Study (Safety Population)

System Organ Class[a] Preferred Term	280 µg/kg QD (N=33) n (%)	280 µg/kg BID (N=10) n (%)	Any Dose (N=33) n (%)
Number of Participants with at Least 1 TEAE Leading to Permanent Treatment Discontinuation	9 (27.3)	1 (10.0)	10 (30.3)
Gastrointestinal disorders	1 (3.0)	0	1 (3.0)
Pancreatitis	1 (3.0)	0	1 (3.0)
General disorders and administration site conditions	2 (6.1)	0	2 (6.1)
Disease progression	2 (6.1)	0	2 (6.1)
Hepatobiliary disorders	1 (3.0)	0	1 (3.0)
Hepatic mass	1 (3.0)	0	1 (3.0)
Investigations	5 (15.2)	0	5 (15.2)
Blood bilirubin increased	4 (12.1)	0	4 (12.1)
Vitamin E decreased	1 (3.0)	0	1 (3.0)
Skin and subcutaneous tissue disorders	0	1 (10.0)	1 (3.0)
Pruritus	0	1 (10.0)	1 (3.0)

Source: Appendix 8.1, Table 14.3.2.8
Abbreviations: AE = adverse event; BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; n = number in a given category; N = number of participants; QD = once daily; TEAE = treatment-emergent adverse event
a Adverse events were coded using MedDRA version 22.1.
Note: Percentages are 100*n/N. The 280 QD dose included all QD doses ≤280 µg/kg. The 280 BID dose included the dose of 420 µg/kg daily for 2 weeks as part of a dose-escalation. For each MRX dose group, the percent of participants was derived using a denominator based on the number of participants that received the given dose. In presenting AEs by MRX dose, events were only counted in the MRX dose group in which the start of the event occurred. Participants were counted only once for each System Organ Class and Preferred Term. Treatment-emergent adverse events are AEs with a start date on or after the first dose of study drug and started prior to the last dose of study drug plus 14 days. 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

Plots of treatment-emergent AESIs over time by PT and individual participant are presented in Appendix 8.1, Figure 14.3.2.

Narratives for participants who had treatment-emergent AESIs are provided in Appendix 10.

5.2.1.6.1. Diarrhea Events

In the overall study population, 20 (60.6%) participants had at least 1 diarrhea event (Appendix 8.2, Listing 16.8.2.2), of which Grade ≥3 events were reported in 3 (9.1%) participants. The diarrhea events included the following: 19 participants (57.6%) with diarrhea; 5 participants (15.2%) with gastroenteritis, and 1 participant (3.0%) with hemorrhagic diarrhea (Appendix 8.1, Table 14.3.2.2).

Details for each diarrhea event are provided in Appendix 8.2, Listing 16.8.2.2. A list of all PTs included for AESI for diarrhea events is found in the SAP Amendment 3 (Appendix 9.9).

5.2.1.6.2. Fat-soluble Vitamin Deficiency Events

A total of 22 participants (66.7%) experienced TEAEs of special interest that were fat-soluble vitamin deficiency events (Table 5-11), of which Grade ≥3 events were reported in 2 (6.1%) participants (Appendix 8.2, Listing 16.8.2.1). The most frequently reported events included the following: epistaxis (9 participants [27.3%]); INR increased (7 participants [21.2%]); irritability (5 participants [15.2%]); fatigue and vitamin D deficiency (4 participants [12.1%] each); and vitamin E decreased, hematochezia, INR abnormal, and alopecia (2 participants [6.1%] each). The remaining TEAEs that were fat-soluble vitamin deficiency events were experienced by no more than 1 participant each.

Details for each fat-soluble vitamin deficiency event are provided in Appendix 8.2, Listing 16.8.2.1. A list of all PTs included for AESI for fat-soluble vitamin deficiency is found in the SAP Amendment 3 (Appendix 9.9).

Table 5-11: Incidence of Treatment-emergent Adverse Events of Special Interest – Fat-soluble Vitamin Deficiency Events During the Study (Safety Population)

System Organ Class Preferred Term	280 µg/kg QD (N=33) n (%)	280 µg/kg BID (N=10) n (%)	Any Dose (N=33) n (%)
Number of Participants with at Least 1 TEAE	22 (66.7)	4 (40.0)	22 (66.7)
Cardiac disorders	1 (3.0)	0	1 (3.0)
Tachycardia	1 (3.0)	0	1 (3.0)
Gastrointestinal disorders	2 (6.1)	1 (10.0)	3 (9.1)
Haematochezia	1 (3.0)	1 (10.0)	2 (6.1)
Melaena	1 (3.0)	0	1 (3.0)
General disorders and administration site conditions	3 (9.1)	1 (10.0)	4 (12.1)
Fatigue	3 (9.1)	1 (10.0)	4 (12.1)
Investigations	9 (27.3)	1 (10.0)	9 (27.3)
International normalised ratio increased	7 (21.2)	1 (10.0)	7 (21.2)
International normalised ratio abnormal	2 (6.1)	0	2 (6.1)
Vitamin E decreased	2 (6.1)	0	2 (6.1)
Platelet count decreased	1 (3.0)	0	1 (3.0)
Vitamin D decreased	1 (3.0)	0	1 (3.0)
Metabolism and nutrition disorders	4 (12.1)	1 (10.0)	4 (12.1)
Vitamin D deficiency	4 (12.1)	0	4 (12.1)
Vitamin E deficiency	1 (3.0)	0	1 (3.0)
Vitamin K deficiency	0	1 (10.0)	1 (3.0)
Musculoskeletal and connective tissue disorders	1 (3.0)	0	1 (3.0)
Muscle spasms	1 (3.0)	0	1 (3.0)
Nervous system disorders	1 (3.0)	0	1 (3.0)
Seizure	1 (3.0)	0	1 (3.0)
Psychiatric disorders	6 (18.2)	1 (10.0)	6 (18.2)
Irritability	5 (15.2)	1 (10.0)	5 (15.2)
Anxiety	1 (3.0)	0	1 (3.0)

System Organ Class Preferred Term	280 µg/kg QD (N=33) n (%)	280 µg/kg BID (N=10) n (%)	Any Dose (N=33) n (%)
Respiratory, thoracic and mediastinal disorders	9 (27.3)	0	9 (27.3)
Epistaxis	9 (27.3)	0	9 (27.3)
Skin and subcutaneous tissue disorders	2 (6.1)	1 (10.0)	3 (9.1)
Alopecia	1 (3.0)	1 (10.0)	2 (6.1)
Dry skin	1 (3.0)	0	1 (3.0)

Source: Appendix 8.1, Table 14.3.2.9
Abbreviations: AE = adverse event; BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; n = number in a given category; N = number of participants; QD = once daily; TEAE = treatment-emergent adverse event
a Adverse events were coded using MedDRA version 22.1.
Note: Percentages are 100*n/N. The 280 QD dose included all QD doses ≤280 µg/kg. The 280 BID dose included the dose of 420 µg/kg daily for 2 weeks as part of a dose-escalation. For each MRX dose group, the percent of participants was derived using a denominator based on the number of participants that received the given dose. In presenting AEs by MRX dose, events were only counted in the MRX dose group in which the start of the event occurred. Participants were counted only once for each System Organ Class and Preferred Term. Treatment-emergent adverse events are AEs with a start date on or after the first dose of study drug and started prior to the last dose of study drug plus 14 days. 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. Elevated Transaminases Events

In the overall study population, 3 (9.1%) participants had at least 1 elevated transaminases event (Appendix 8.2, Listing 16.8.2.3), of which Grade ≥3 events were reported in 2 (6.1%) participants. All 3 (9.1%) participants experienced increased ALT and increased AST.

Details for each elevated transaminases event are provided in Appendix 8.2, Listing 16.8.2.3. A list of all PTs included for AESI for elevated transaminases is found in the SAP Amendment 3 (Appendix 9.9).

5.2.1.6.4. Elevated Bilirubin Events

In the overall study population, 9 (27.3%) participants had at least 1 elevated bilirubin event (Appendix 8.2, Listing 16.8.2.4), of which Grade ≥3 events were reported in 6 (18.2%) participants. The elevated bilirubin events included the following: 6 participants (18.2%) with increased blood bilirubin, 3 participants (9.1%) with hyperbilirubinemia, and 1 participant (3.0%) with increased conjugated bilirubin.

Details for each elevated bilirubin event are provided in Appendix 8.2, Listing 16.8.2.4. A list of all PTs included for AESI for elevated bilirubin events is found in the SAP Amendment 3 (Appendix 9.9).

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), with a summary of corrected sodium included in Appendix 8.1, Table 14.3.3.11. The summaries include mean, 95% CIs, SD, SE, median, minimum, and maximum results of clinical chemistry and hematology parameters in the Safety Population by analysis visit. The changes and percent changes in assessments from baseline to each analysis visit are also given.

As was reported in the LUM001-501 Final CSR using data through Week 72, 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.

The following abnormal results in the category of fat-soluble vitamins were reported as AEs in the investigations SOC during study (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 4 participants (12.1%), of Grade 1 severity
- Vitamin E deficiency – reported in 1 participant (3.0%), of Grade 1 severity
- Vitamin K deficiency – reported in 1 participant (3.0%), of Grade 1 severity

Appendix 8.1, Table 14.3.3.11 presents a summary of fat-soluble vitamin level abnormalities in the Safety Population. The majority of participants in the overall study population, in general, had sufficient 25-hydroxyvitamin D levels, INR, retinol:RBP molar ratio, and Vitamin A levels, and a sufficient alpha tocopherol/total lipids ratio from Week 132 onwards.

5.2.2.1.2. Hematology

Appendix 8.1, Table 14.3.3.2 presents mean, 95% CIs, SD, SE, 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 abnormalities of the hematology profile were reported as TEAEs during the study (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
- Hemoglobin 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. Total cholesterol and LDL-C were assessed as exploratory efficacy endpoints in this study; these data are presented in Appendix 8.1, Tables 14.2.10.1 (total cholesterol), 14.2.10.2 (total cholesterol by PFIC2 subtype), 14.2.13.1 (LDL-C), and 14.2.13.2 (LDL-C by PFIC2 subtype).

By-participant listings for HDL-C and triglycerides are provided in Appendix 8.2, Listing 16.10.5.

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.

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, activated partial thromboplastin time, and PT were assessed as exploratory efficacy endpoints in this study.

The following results in the coagulation studies triggered a TEAE during the study (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 Appendix 8.1, Table 14.3.3.9.1. Past Week 108, no participants had meaningful shifts from baseline in bilirubin; with the exception of 1 participant with PFIC2 at Week 4, no participants had meaningful shifts from baseline in ALT.

A by-participant listing of fat-soluble vitamin levels with significant shifts from baseline over the study is presented in Appendix 8.1, Table 14.3.3.8.

There were few notable shifts from baseline in the fat-soluble vitamins (Appendix 8.1, Table 14.3.3.12). Up to 33.3% of participants showed a clinically meaningful shift from baseline in 25-hydroxyvitamin D between Week 8 and Week 120. After a period of no participants experiencing clinically meaningful shifts from baseline in 25-hydroxyvitamin D from

Week 124/LOCF, 12.5%, 22.2%, and 50.0% of participants experienced clinically meaningful shifts from baseline in 25-hydroxyvitamin D at Weeks 228, 240, and 276, respectively.

Between 12.5% and 30.0% of participants experienced clinically meaningful shifts from baseline in their alpha tocopherol / total lipids ratio between Weeks 8 and 180. From Week 192 onwards, no clinically meaningful shifts from baseline in alpha tocopherol / total lipids ratio were recorded.

From Week 8 to Week 96, up to 7.7% of participants experienced clinically meaningful shifts from baseline in INR. From Week 108 onwards, no further clinically meaningful shifts from baseline in INR were observed.

Throughout the study, the number of participants experiencing clinically meaningful shifts from baseline in their retinol:RBP molar ratio ranged from 0.0% to 44.4%, with 2/2 and 1/2 participants experiencing a clinically meaningful shift at Week 276 and 288, respectively. Clinically meaningful shifts from baseline were not observed in any participant at 10 of the 27 analysis visits.

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 study (Appendix 8.1, Table 14.3.2.2):

- Blood bilirubin increased – reported in 6 participants (18.2%), 1 of Grade 2 and 3 of Grade 3 severity
- Alanine aminotransferase increased – reported in 3 participants (9.1%), 1 each of Grade 2, Grade 3 and Grade 4 severity
- Aspartate aminotransferase increased – reported in 3 participants (9.1%), 2 of Grade 2 and 1 of Grade 4 severity
- Bilirubin conjugated increased – reported in 1 participant (3.0%), of Grade 3 severity
- Blood bicarbonate decreased – reported in 1 participant (3.0%), of Grade 1 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 is provided in Appendix 8.1, Table 14.3.3.10.

5.2.3. Other Safety Evaluations

5.2.3.1. Vital Signs

By-participant vital signs are presented in Appendix 8.2, Listing 16.9.1.

5.3. Palatability

Palatability data was collected at each clinic visit in the follow-up treatment period. Overall, caregiver responses were missing in the majority of time points assessed (80.0% to 100.0% missing at least on 1 week) (Appendix 8.1, Table 14.4). For child only or child and caregiver responses, no clear pattern was seen in the number of participants rating the taste of medicine immediately or after 5 minutes, with consistent percentage of participants rating the taste between 1 and 5. At most visits, the majority of participants (≥60%) noted that they would take the medication every day.

By-participant palatability questionnaire data are found in Appendix 8.2, Listing 16.14.

5.4. Pharmacokinetics

Appendix 8.1, Table 14.3.5 provides a summary of plasma sample maralixibat concentrations by analysis visit for the overall Safety Population. Individual participant plasma concentration data are presented in Appendix 8.2, Listing 16.13; however, due to poor absorption of maralixibat, very low systemic exposure and plasma drug levels were found. Hence, a formal pharmacokinetic analysis could not be conducted.

5.5. Pharmacodynamics

Not applicable

5.6. Genetics

A by-participant genotype listing is available in Appendix 8.2, Listing 16.12.

5.7. Metabolomic and Proteomic Analysis

Exploratory responder analyses (metabolomics and proteomic investigation) was outside the scope of the analysis.

5.8. Immunogenicity

Not applicable.

5.9. Health Economics

Not applicable.

6. OVERALL CONCLUSIONS

- Improvements in pruritus previously reported at 48 weeks of treatment with MRX continued throughout the study. Numerical improvement was observed in participants with PFIC2 and PFIC1 in ItchRO(Obs) weekly morning average, weekly average, and weekly evening average scores. Improvements were greater in participants with PFIC2 than those with PFIC1, and generally, participants with nt-PFIC2 showed a better response than those with t-PFIC2.
- Previously reported numerical reductions in sBA observed at 13 weeks and 72 weeks of treatment with MRX in participants with PFIC2 continued throughout the study. These improvements in sBA levels were not evident in participants with PFIC1.
- The numerical improvement in ALT described for participants with PFIC2 in the LUM001-501 Final CSR continued throughout the study. A numerical improvement in AST was also observed. These improvements were not observed in participants with PFIC1.
- Previously reported numerical increases in total bilirubin and direct bilirubin from baseline to 72 weeks of treatment in participants with PFIC2 and PFIC1 were not sustained long term; by Week 204 total bilirubin levels had returned to close to baseline (participants with nt-PFIC2) or showed a reduction (improvement) (participants with PFIC1), and by Week 204 direct bilirubin levels showed a reduction (improvement) from baseline (participants with nt-PFIC2 and PFIC1).
- The change from baseline in height, weight, and BMI z-scores was not statistically significant regardless of analysis visit, in participants with PFIC1, PFIC2, or in the overall study population, with the exception of the BMI z-scores at 2 analysis visits (for participants with PFIC2 at Week 2 and Week 252, and participants with PFIC1 at Week 252).
- In posthoc analyses performed, 7/19 participants with nt-PFIC2 experienced control of the sBA levels to below 102 µmol/L or a 75% reduction from baseline resulting in clinically meaningful reductions in pruritus (≥1.0 reduction in ItchRO(Obs) or score below 1.0), normalization of bilirubin, ALT, and AST if elevated, and improvement in height z-score. These responses happened at both 280 µg/kg once daily and 280 µg/kg twice daily dosing of MRX. All 7 of these participants demonstrating this response to maralixibat treatment remained on the study for over 5 years.
- Serious AEs were experienced by 15 participants (45.5%) during the study. The only SAEs reported for more than 1 participant were abdominal pain, diarrhea, and gastroenteritis, 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. No SAEs were experienced by participants on a dose of MRX of 280 µg/kg BID.
- Overall, reported TEAEs were generally mild or moderate in severity.

- Fourteen participants (42.4%) experienced CTCAE Grade 3 or CTCAE Grade 4 TEAEs during the study. A total of 12 participants (36.4%) experienced TEAEs of maximum severity Grade 3. A Grade 4 event of hyperbilirubinemia (considered potentially related to study drug) was experienced by 1 participant while Grade 4 events of ALT increased and 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 26 participants (78.8%) overall.
- The most common TEAEs reported included the following: pyrexia (20 participants [60.6%]), diarrhea (19 participants [57.6%]), cough (18 participants [54.5%]), and vomiting (17 participants [51.5%]).
- A total of 10 participants (30.3%) experienced TEAEs that led to permanent treatment discontinuation. Treatment-emergent AEs leading to permanent treatment discontinuation in more than 1 participant were reported as blood bilirubin increased and disease progression.
- No deaths were reported in the study.
- Long-term safety data presented here were consistent with those reported in the LUM001-501 Final CSR, during the first 72 weeks of treatment with MRX.
- Overall, MRX was safe and well tolerated.