surviving through the age of 18. PFIC 2 is associated with a continuous progressive course of symptoms. While extrahepatic involvement such as pancreatitis or diarrhea can be a feature of PFIC 1, the initial presentation and evolution of the disease in PFIC 2 tends to be more severe than in PFIC 1, with persistent jaundice occurring within the first months of life and rapid progression to cirrhosis and liver failure within the first years of life. Interruption of the entero-hepatic circulation of bile acids through partial external biliary diversion (PEBD) surgery can lead to promising results with respect to pruritus, jaundice, and histology, both in patients with PFIC 1 and PFIC 2. A previous study reported a dramatic 1-year outcome in patients undergoing PEBD with 13/21 (62%) of patients normalizing serum bile acids (sBAs) and liver function; however, other groups have reported overall failure rates of PEBD of up to 30% with 30%-50% of patients requiring repeat surgery. Additionally, PEBD must be performed before liver fibrosis and cirrhosis are established for optimal benefit. For the vast majority of patients who do not undergo PEBD or do not respond, liver transplantation may be the only treatment option. Given the clinical outcomes associated with PFIC, including the profound negative impact on patients' and caregivers' quality of life, and the fact that there are no approved treatments, there is a clear unmet medical need for a novel treatment for this disease.

[0005] Maralixibat (as maralixibat chloride) is currently the only approved medication to treat pruritus in people with Alagille syndrome. It is known that maralixibat chloride inhibits apical sodium co-dependent bile acid transport (U.S. Pat. No. 5,994,391). The synthesis of maralixibat chloride is previously disclosed in U.S. patent application Pub. No. 2003/0199515A1.

SUMMARY

[0006] Various non-limiting examples of the disclosure are described below.

[0006a] In an aspect, there is provided the use of maralixibat, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a progressive familial intrahepatic cholestasis (PFIC) in a subject in need thereof, wherein the maralixibat or pharmaceutically acceptable salt thereof is to be administered in an amount from about 600 μg/kg/day to about 1400 μg/kg/day.

[0006b] In another aspect, there is provided the use of a pharmaceutical composition comprising maralixibat, or a pharmaceutically acceptable salt thereof, an antioxidant, and a preservative in the manufacture of a medicament for treating a progressive familial intrahepatic cholestasis (PFIC) in a subject in need thereof.

[0007] In one example, the present disclosure provides a method for treating a progressive familial intrahepatic cholestasis (PFIC) in a subject in need thereof comprising administering to the subject maralixibat, or a pharmaceutically acceptable salt thereof.

[0008] In one example, the pharmaceutically acceptable salt of maralixibat is maralixibat chloride, maralixibat bromide, maralixibat acetate, or maralixibat mesylate. In one example, the pharmaceutically acceptable salt of maralixibat is maralixibat chloride.

[0009] In one example, the maralixibat or pharmaceutically acceptable salt thereof is administered in an amount from about 10 μg/kg/day to about 1400 μg/kg/day. In one

example, the maralixibat or pharmaceutically acceptable salt thereof is administered in an amount from about 300 μg/kg/day to about 1200 μg/kg/day. In one example, the maralixibat or pharmaceutically acceptable salt thereof is administered in an amount from about 600 μg/kg/day to about 1200 μg/kg/day. In one example, the maralixibat or pharmaceutically acceptable salt thereof is maralixibat chloride, and maralixibat chloride is administered in an amount of about 1200 μg/kg/day.

[0010] In one example, the maralixibat or pharmaceutically acceptable salt thereof is administered in an amount of about 0.5 mg/day to about 100 mg/day.

[0011] In one example, the PFIC is PFIC 1, PFIC 2, PFIC 3, PFIC 4, PFIC 5, or PFIC 6. In one example, the PFIC is PFIC 1. In one example, the PFIC is PFIC 2. In one example, the PFIC 2 is non-truncated PFIC 2. In one example, the PFIC 2 is truncated PFIC 2. In one example, the PFIC is PFIC 3. In one example, the PFIC is PFIC 4. In one example, the PFIC is PFIC 5. In one example, the PFIC is PFIC 6.

[0012] In one example, the PFIC is heterozygous. In one example, the subject has intermittent cholestasis. In one example, the subject has undergone biliary divergion surgery.

[0013] In one example, the subject is a pediatric subject. In one example, the subject is more than 1 year old and less than 18 years old. In one example, the subject is less than 12 months old.

[0014] In one example, the subject has a mutation in a gene selected from the group consisting of: *ATP8B1*, *ABCB11*, *ABCB4*, *TJP2*, *NR1H4*, and *MYO5B*.

[0015] In one example, the maralixibat or pharmaceutically acceptable salt thereof is administered once daily (QD). In one example, the maralixibat or pharmaceutically acceptable salt thereof is administered twice daily (BID).

[0016] In one example, the maralixibat or pharmaceutically acceptable salt thereof is maralixibat chloride, and maralixibat chloride is administered at 600 μg/kg/day BID for a total daily dose of 1200 μg/kg/day.

[0017] In one example, the administration of the maralixibat or pharmaceutically acceptable salt thereof results in the reduction in a symptom or a change in a disease-relevant laboratory measure of PFIC that is maintained for at least 2 months. In one example, the administration of the maralixibat or pharmaceutically acceptable salt thereof results in the reduction in a symptom or a change in a disease-relevant laboratory measure of PFIC that is

maintained for at least 4 months. In one example, the administration of the maralixibat or pharmaceutically acceptable salt thereof results in the reduction in a symptom or a change in a disease-relevant laboratory measure of PFIC that is maintained for at least 6 months. In one example, the administration of the maralixibat or pharmaceutically acceptable salt thereof results in the reduction in a symptom or a change in a disease-relevant laboratory measure of PFIC that is maintained for at least 1 year.

[0018] In one example, the reduction in the symptom or the change in the disease-relevant laboratory measure is determined relative to a baseline level.

[0019] In one example, the reduction in the symptom or change in the disease-relevant laboratory measure comprises a reduction in sBA concentration, a reduction in pruritus, a reduction in total bilirubin, a reduction in direct bilirubin, an improvement in growth, or a combination thereof.

[0020] In one example, the administration of the maralixibat reduces intensity of pruritus. In one example, the reduction of intensity of pruritus is a reduction of an ItchRO(Obs) score, of a CSS score, or a combination thereof.

[0021] In one example, the administration of the maralixibat or pharmaceutically acceptable salt thereof results in a reduction of an ItchRO(Obs) score of the subject by at least 1.0 points relative to baseline. In one example, the administration of the maralixibat or pharmaceutically acceptable salt thereof results in a reduction of an ItchRO(Obs) score of the subject by at least 1.2 points relative to baseline. In one example, the administration of the maralixibat or pharmaceutically acceptable salt thereof results in a reduction of an ItchRO(Obs) score of the subject by at least 1.4 points relative to baseline. In one example, the administration of the maralixibat or pharmaceutically acceptable salt thereof results in a reduction of an ItchRO(Obs) score of the subject by at least 1.6 points relative to baseline.

[0022] In one example, the administration of the maralixibat or pharmaceutically acceptable salt thereof results in a reduction of a CSS score of the subject by at least 1.0 points relative to baseline. In one example, the administration of the maralixibat or pharmaceutically acceptable salt thereof results in a reduction of a CSS score of the subject by at least 1.2 points relative to baseline. In one example, the administration of the maralixibat or pharmaceutically acceptable salt thereof results in a reduction of a CSS score of the subject by at least 1.4 points relative to baseline. In one example, the administration of the maralixibat or

pharmaceutically acceptable salt thereof results in a reduction of a CSS score of the subject by at least 1.6 points relative to baseline.

[0023] In one example, the administration of the maralixibat or pharmaceutically acceptable salt thereof results in a reduction in sBA concentration in the subject by at least 50 μmol/L relative to baseline. In one example, the administration of the maralixibat or pharmaceutically acceptable salt thereof results in a reduction in sBA concentration in the subject by at least 100 μmol/L relative to baseline.

[0024] In one example, the administration of the maralixibat or pharmaceutically acceptable salt thereof results in a reduction in total bilirubin. In one example, the administration of the maralixibat or pharmaceutically acceptable salt thereof results in a reduction in total bilirubin of at least 0.2 mg/dL relative to baseline. In one example, the administration of the maralixibat or pharmaceutically acceptable salt thereof results in a reduction in total bilirubin of at least 0.5 mg/dL relative to baseline. In one example, the administration of the maralixibat or pharmaceutically acceptable salt thereof results in a reduction in total bilirubin of at least 1.0 mg/dL relative to baseline.

[0025] In one example, the administration of the maralixibat or pharmaceutically acceptable salt thereof results in a reduction in direct bilirubin. In one example, the administration of the maralixibat or pharmaceutically acceptable salt thereof results in a reduction in direct bilirubin of at least 0.2 mg/dL relative to baseline. In one example, the administration of the maralixibat or pharmaceutically acceptable salt thereof results in a reduction in direct bilirubin of at least 0.5 mg/dL relative to baseline. In one example, the administration of the maralixibat or pharmaceutically acceptable salt thereof results in a reduction in direct bilirubin of at least 1.0 mg/dL relative to baseline.

[0026] In one example, the administration of the maralixibat or pharmaceutically acceptable salt thereof results in an improvement in a height Z-score or a weight Z-score, or both in the subject relative to baseline. In one example, the administration of the maralixibat or pharmaceutically acceptable salt thereof results in an increase in the weight Z-score of at least 0.2 relative to baseline.

[0027] In one example, the method further comprises administering a lipid soluble vitamin (LSV) in subjects with LSV deficiency. In one example, the LSV is selected from the group consisting of Vitamin A, Vitamin D and Vitamin E.

[0028] In one example, the maralixibat or pharmaceutically acceptable salt thereof is administered before a meal. In one example, the maralixibat or pharmaceutically acceptable salt thereof is administered about 30 minutes before a meal. In one example, wherein the maralixibat or pharmaceutically acceptable salt thereof is administered BID, about 30 minutes before the morning meal and about 30 minutes before the evening meal.

[0029] In one example, the maralixibat is administered in the form of a pharmaceutical composition comprising maralixibat, or a pharmaceutically acceptable salt thereof, an antioxidant, and a preservative. In one example, the pharmaceutical composition is a liquid composition for oral administration. In one example, the liquid composition is an aqueous solution.

[0030] In one example, the maralixibat is present in an amount of about 2 mg/mL to about 100 mg/mL of the composition. In one example, the maralixibat is present in an amount of about 5 mg/mL to about 50 mg/mL of the composition. In one example, the maralixibat is present in an amount of about 8 mg/mL to about 20 mg/mL of the composition. In one example, the maralixibat is present in an amount of about 9.5 mg/mL to about 10 mg/mL of the composition.

[0031] In one example, the preservative is an antimicrobial preservative. In one example, the antimicrobial preservative is selected from the group consisting of propylene glycol, ethyl alcohol, glycerin, benzalkonium chloride, benzethonium chloride, benzoic acid, benzyl alcohol, butylparaben, cetrimide (cetyltrimethylammonium bromide), cetrimonium bromide, cetylpyridinium chloride, chlorhexidine, chlorobutanol, chlorocresol, cresol, ethylparaben, methylparaben, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric acetate, phenylmercuric borate, phenylmercuric nitrate, propylparaben, sodium benzoate, sodium dehydroacetate, sodium propionate, sorbic acid, potassium sorbate, thimerosal, thymol, and combinations thereof. In one example, the preservative is propylene glycol. In one example, the preservative is present in an amount from about 30% w/w to about 40% w/w of the composition. In one example, the preservative is present in an amount from about 300 mg/mL to about 400 mg/mL of the composition.

[0032] In one example, the antioxidant is selected from the group consisting of an aminocarboxylic acid, an aminopolycarboxylic acid, ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, sodium ascorbate, sodium

formaldehyde sulfoxylate, sodium metabisulfite, BHT, BHA, sodium bisulfite, vitamin E or a derivative thereof, propyl gallate, and combinations thereof.

[0033] In one example, the antioxidant is an aminopolycarboxylic acid selected from EDTA (ethylenediaminetetraacetic acid), DTPA (diethylenetriaminepentaacetic acid), EGTA (ethylene glycol-bis(β-aminoethyl ether)-N,N,N′,N′-tetraacetic acid), NTA (nitrilotriacetic acid), BAPTA (1,2-bis(o-aminophenoxy)ethane-N,N,N′,N′-tetraacetic acid), NOTA (2,2',2"-(1,4,7-triazonane-1,4,7-triyl)triacetic acid), DOTA (tetracarboxylic acid), and EDDHA (ethylenediamine-N,N′-bis(2-hydroxyphenylacetic acid). In one example, the antioxidant is EDTA. In one example, the antioxidant is present in an amount of about 0.01% w/w to about 0.5% w/w of the composition.

[0034] In one example, the pharmaceutical composition further comprises a sweetener, a taste-masking ingredient, or a combination thereof.

[0035] In one example, the pharmaceutical composition comprises:

a. from about 8 mg/mL to about 20 mg/mL of maralixibat;
b. from about 330 mg/mL to about 380 mg/mL of propylene glycol;
c. about 1 mg/mL of disodium EDTA;
d. a sweetener, a taste-masking ingredient, or a combination thereof, and
e. water.

[0036] These and other examples of the present disclosure will become apparent to those skilled in the art after a reading of the following detailed description of the disclosure, including the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0037] **Figure 1** provides a schematic diagram summarizing physiological effects of maralixibat administration in a patient. IBAT, ileal bile acid transporter.

[0038] **Figure 2 s**hows a schematic providing an overview of a dosing regimen used in a phase 3 open-label extension clinical study of maralixibat in subjects with PFIC. The clinical study investigated long-term exposure to maralixibat.

[0039] **Figure 3** shows a flow diagram representing the protocol recommendations for treatment of and discontinuation due to worsening of LSV deficiency.

Table 1. Schedule of Assessments

Procedures	Screening [a]	Dose Escalation (4-6 weeks)						Stable Dosing (20-22 weeks)											Follow-up
Visit/Subject Contact #	**Screening / V0**	**Baseline / V1**	**Subject contact**	**V2**	**Subject contact**	**V3**	**Subject contact**	**V4**	**Subject contact**	**V5**	**Subject contact**	**V6**	**Subject contact**	**V7**	**Subject contact**	**V8**	**Subject contact**	**EOT/ET V9 [b]**	
Study Week	**-6**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**27**
Study Day	**Day -42**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**56**	**70**	**84**	**98**	**112**	**126**	**140**	**154**	**168**	**182**	**189**
Window (in days)	**(-5)**		**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±2)**
Informed Consent/Assent	X																		
Eligibility Assessment	X	X																	
Demographics	X																		
Medical History	X																		
Physical & Vital signs [c]	X	X		X		X		X		X		X		X		X		X	
ECG	X	X								X								X	
Liver Ultrasound [d]	X																	X	
Pregnancy Test [e]	S	U				U		U		U		U		U		U		S	
Confirm PFIC Genotype Results [f]	X																		
eDiary Device Provided / Returned [g]	P																	R	
ItchRO(Obs), ItchRO(Pt) & EDQ	Twice-daily completion of ItchRO & EDQ																		
Review eDiary & Assess Compliance		X		X		X		X		X		X		X		X		X	
Randomized		X																	
CIS [h]		X				X		X		X		X		X		X		X	
PIS [i]		X				X		X		X		X		X		X		X	
PIC																		X	
CIC																		X	
PedsQL [j]		X				X		X		X		X		X		X		X	

Procedures	Screening [a]	Dose Escalation (4-6 weeks)						Stable Dosing (20-22 weeks)											Follow-up
Visit/Subject Contact #	**Screening / V0**	**Baseline / V1**	**Subject contact**	**V2**	**Subject contact**	**V3**	**Subject contact**	**V4**	**Subject contact**	**V5**	**Subject contact**	**V6**	**Subject contact**	**V7**	**Subject contact**	**V8**	**Subject contact**	**EOT/ET V9[b]**	
Study Week	**-6**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**27**
Study Day	**Day -42**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**56**	**70**	**84**	**98**	**112**	**126**	**140**	**154**	**168**	**182**	**189**
Window (in days)	**(-5)**		**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±2)**
Clinician Scratch Scale	X	X		X		X		X		X		X		X		X		X	
CBC with Differential	X	X		X				X		X		X		X		X		X	
Coagulation	X	X		X				X		X		X		X		X		X	
Chemistry Panel	X	X		X				X		X		X		X		X		X	
Lipid Panel[k]	X	X		X				X		X		X		X		X		X	
Urinalysis		X						X		X				X				X	
FGF-19, Autotaxin, C4[k]		X						X		X				X				X	
sBA collection[k]	X	X		X				X		X		X		X		X		X	
Lipid Soluble Vitamins[k,l]		X						X		X		X		X		X		X	
AFP Sample		X								X								X	
PK Sample[m]										X								X	
Serum storage sample		X		X				X		X		X		X		X		X	
Healthcare Utilization				X				X		X		X		X		X		X	X
Study Medication Supplied[n]		X		X		X		X		X		X		X		X			
Study Medication Administration[o]		Twice-daily administration																	
Assess AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and Concomitant Treatments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AFP=a-fetoprotein; C4=7a-hydroxy-4-cholesten-3-one; CBC=complete blood count; CIS=Caregiver Impression of Severity; CIC=Caregiver Impression of Change; ECG=electrocardiogram; EDQ=exploratory diary questionnaire; EOT=end of treatment; ET=early termination; FGF-19=fibroblast growth factor-19; ItchRO=Itch Reported Outcome; P=Provided; PedsQL=Pediatric Quality of Life Inventory; PIC=Patient Impression of Change; PIS=Patient Impression of Severity of Pruritus; PK=pharmacokinetic; R=Returned; S=Serum; U= Urine; V=visit

[a] Subjects who initially fail to meet eligibility criteria may be re-assessed during the 6-week screening period prior to being captured as a screen failure. Subjects may also be re-screened.

skin as a result of scratching as observed by the physician. The CSS uses a 5-point scale, in which 0 designates no evidence of scratching and 4 designates cutaneous mutilation with bleeding, hemorrhage and scarring. A clinician's assessment of pruritus made by the principal investigator or sub-investigator using the CSS was recorded at screening, baseline, and at additional study visits as outline in **Table 2.**

Table 2. List of Laboratory Analytes

Serum β-hCG (if indicated)	**Clinical Chemistry**	**Lipid Panel**[a]	**Urinalysis**
CBC with Differential	Albumin	Total cholesterol	pH
Hematocrit	ALP	LDL-C (direct)	Specific gravity
Hemoglobin	Amylase	HDL-C	Protein
MCV, MCH, MCHC	ALT (SGPT)	Triglycerides (TG)	Glucose
Red blood cells	AST (SGOT)	**Cholestasis Biomarkers**[a]	Ketones
Platelets	Bicarbonate	Total serum bile acids (sBA)	Bilirubin
White blood cells	Bilirubin, direct (conjugated)	Serum bile acid subspecies	Occult blood and cells
WBC Differential (% and absolute)	Total serum bilirubin (TSB)	7α-hydroxy-4-cholesten-3-one (C4)	Nitrite
Neutrophils	Blood urea nitrogen (BUN)	FGF-19	Urobilinogen
Eosinophils	Calcium	Autotaxin	Leukocyte esterase
Basophils	Chloride	**Lipid Soluble Vitamins**[a]	Microscopic examination[b]
Lymphocytes	Creatinine	25-hydroxy vitamin D	Oxalate
Monocytes	GGT	Retinol	Urinary creatinine
Coagulation	Glucose	Retinol binding protein (RBP)	**Maralixibat Levels**
aPTT (sec)	Lipase	α-Tocopherol	Maralixibat in plasma
INR	Phosphate		**Marker of hepatocellular carcinoma**
PT (sec)	Potassium		α-Fetoprotein (AFP)
	Sodium		
	Total protein		
	Uric Acid		
	Measured serum Osmolality		

AFP=α-fetoprotein; ALP=alkaline phosphatase; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; β-hCG=beta human chorionic gonadotropin; FGF-19=fibroblast growth factor 19; FIB-4=fibrosis-4; GGT=gamma-glutamyl transferase; PT=prothrombin time; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBP=Retinol binding protein: SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; WBC=white blood cell.

[a] Blood samples for the analysis of cholestasis biomarkers, lipid panel and lipid soluble vitamins should be drawn prior to administration of vitamin supplementation and as much as possible approximately 6 hours after food or formula (water intake is permitted if necessary but not recommended). Other biomarkers [e.g., lysophosphatidic acid (LPA),] may be measured. At the discretion of the sponsor, samples will be collected and appropriately stored for subsequent analysis, as needed.

[b] Will be performed on abnormal findings unless otherwise specified.

Table 3. Demographics for participants in the clinical study

Status or Category	Primary Cohort Maralixibat (N=14)	Primary Cohort Placebo (N=17)	Primary Cohort Overall (N=31)	PFIC Cohort Maralixibat (N=33)	PFIC Cohort Placebo (N=31)	PFIC Cohort Overall (N=64)	All Subjects Maralixibat (N=47)	All Subjects Placebo (N=46)	All Subjects Overall (N=125)
Screened for Eligibility									125
Screen Failure									32
Randomized	14	17	31	33	31	64	47	46	93
Total Number of Siblings	2	0	2	4	4	8	4	6	10
Safety Population	14	17	31	33	31	64	47	46	93
ITT Population	14 (100.0%)	17 (100.0%)	31 (100.0%)	33 (100.0%)	31 (100.0%)	64 (100.0%)	47 (100.0%)	46 (100.0%)	93 (100.0%)
Per-Protocol Population	9 (64.3%)	17 (100.0%)	26 (83.9%)	27 (81.8%)	31 (100.0%)	58 (90.6%)	41 (87.2%)	45 (97.8%)	86 (92.5%)
Completed Study Treatment	13 (92.9%)	15 (88.2%)	28 (90.3%)	32 (97.0%)	28 (90.3%)	60 (93.8%)	44 (93.6%)	42 (91.3%)	86 (92.5%)
Discontinued Early	1 (7.1%)	2 (11.8%)	3 (9.7%)	1 (3.0%)	3 (9.7%)	4 (6.3%)	3 (6.4%)	4 (8.7%)	7 (7.5%)
Reason for Discontinuation	0	0	0	0	0	0	1 (2.1%)	0	1 (1.1%)
Adverse Event	0	0	0	0	0	0	0	0	0
Death	0	0	0	0	0	0	0	0	0
Lost to follow-up	0	0	0	0	0	0	0	0	0
Non-compliance with study drug	0	0	0	0	0	0	0	0	0
Lack of efficacy	0	0	0	0	0	0	0	0	0
Physician decision	0	0	0	0	0	0	0	0	0
Pregnancy	0	0	0	0	0	0	0	0	0
Liver transplant	0	0	0	0	0	0	1 (2.1%)	0	1 (1.1%)
PEBD surgery	0	0	0	0	0	0	0	0	0
Protocol violation	0	0	0	0	0	0	0	0	0
Withdrawal of consent	1 (7.1%)	1 (5.9%)	1 (6.5%)	1 (3.0%)	2 (6.5%)	3 (4.7%)	1 (2.1%)	3 (6.5%)	4 (4.3%)
Study terminated by sponsor	0	0	0	0	0	0	0	0	0
Disease progression	0	1 (5.9%)	1 (3.2%)	0	1 (3.2%)	1 (1.6%)	0	1 (2.2%)	1 (1.1%)
Other	0	0	0	0	0	0	0	0	0

[1] Age at baseline visit.
[2] Height, weight, and BMI Z-scores are based on a subject's sex and age at the baseline visit. The World Health Organization (WHO) growth charts were used to derive Z-scores for subjects less than 24 months old and the Center for Disease Control (CDC) growth charts were used to derive Z-scores for subjects equal to or greater than 24 months old.

Table 4. Baseline disease characteristics for participants in the clinical study

Variable	Statistic or Category	Primary Cohort			PFIC Cohort			All Subjects		
		Maralixibat (N=14)	Placebo (N=17)	Overall (N=31)	Maralixibat (N=33)	Placebo (N=31)	Overall (N=64)	Maralixibat (N=47)	Placebo (N=46)	Overall (N=93)
Clinician Scratch Scale (CSS) Score	Mean	2.8	2.5	2.6	2.8	2.6	2.7	2.7	2.7	2.7
	0	0	0	0	0	0	0	1 (2.1%)	0	1 (1.1%)
	1	0	3 (17.6%)	3 (9.71%)	1 (3.0%)	6 (19.4%)	7 (10.9%)	1 (2.1%)	6 (13.0%)	7 (7.5%)
	2	6 (42.9%)	4 (23.5%)	10 (32.3%)	10 (30.3%)	5 (16.1%)	15 (23.4%)	15 (31.9%)	10 (21.7%)	25 (26.9%)
	3	5 (35.7%)	8 (47.1%)	13 (41.9%)	17 (51.5%)	15 (48.4%)	32 (50.0%)	22 (46.8%)	20 (43.5%)	42 (45.2%)
	4	3 (21.4%)	2 (11.8%)	5 (16.1%)	5 (15.2%)	5 (16.1%)	10 (15.6%)	8 (17.0%)	10 (21.7%)	18 (19.4%)
ItchRO (Obs) 4-wk Morning Avg Severity Score	Mean	2.876	2.611	2.731	2.850	2.732	2.793	2.842	2.921	2.881
ItchRO (Obs) 4-wk Evening Avg Severity Score	Mean	2.823	2.554	2.676	2.794	2.657	2.728	2.786	2.812	2.799
ItchRO (Obs) 4-wk Highest Daily Avg Severity Score	Mean	3.029	2.796	2.901	3.010	2.877	2.945	2.995	3.051	3.023
Time Since Original Diagnosis of PFIC (months)	Mean	45.9	33.5	39.1	34.3	27.5	31.0	31.7	32.7	32.2
Baseline UDCA Usage	Mean	11 (78.6%)	17(100.0%)	28 (90.3%)	27 (81.8%)	30 (96.8%)	57 (89.1%)	39 (83.0%)	39 (84.8%)	78 (83.9%)
Baseline Rifampicin Usage	Mean	6 (42.9%)	9 (52.9%)	15 (48.4%)	18 (54.5%)	15 (48.4%)	33 (51.6%)	26 (55.3%)	23 (50.0%)	49 (52.7%)
Total Serum Bile Acid (umol/L)	Mean	331.879	312.278	312.113	254.327	272.297	263.312	262.615	243.306	252.854
Alkaline Phosphatase (U/L)	Mean	535.75	442.89	484.83	630.14	517.73	575.69	594.87	512.85	554.30
Aspartate Aminotransferase (U/L)	Mean	103.75	158.07	133.54	96.89	129.81	112.84	119.65	125.58	122.58
Alanine Aminotransferase (U/L)	Mean	98.39	154.91	129.39	87.83	127.34	106.97	107.86	121.23	114.47
Total Bilirubin (mg/dL)	Mean	3.475	2.714	3.058	4.118	4.041	4.081	4.099	3.796	3.950
Direct Bilirubin (mg/dL)	Mean	2.421	1.919	2.146	2.979	2.934	2.957	2.989	2.769	2.880
GGT (U/L)	Mean	18.43	22.28	20.54	64.91	70.33	67.54	51.56	59.45	55.46
Albumin (g/dL)	Mean	4.561	4.875	4.733	4.573	4.717	4.643	4.667	4.686	4.676

Table 5. Baseline Characteristics and Demographics Between the Cohorts

Variable	BSEEP		All-PFIC		Full Study	
	Maralixibat (n = 14)	Placebo (n=17)	Maralixibat (n = 33)	Placebo (n=31)	Maralixibat (n = 47)	Placebo (n=46)
Age (years); mean	6.3	4.2	4.9	4.4	4.8	4.7
Sex (male); %	50	35	52	42	43	48
Pruritus (ItchRO[Obs]); mean	2.9	2.6	2.9	2.7	2.8	2.9
Total sBA (|imol/L); mean	312	312	254	272	263	243
UDCA usage (%)	79	100	82	97	83	85
Rifampicin usage (%)	43	53	55	48	55	50
Alanine aminotransferase (U/L); mean	98.4	154.9	87.8	127.3	107.9	121.2
Total bilirubin (mg/dL); mean	3.5	2.7	4.1	4.0	4.1	3.8
Direct bilirubin (mg/dL); mean	2.4	1.9	3.0	2.9	3.0	2.8
Height Z-score; mean	-2.0	-2.2	-2.1	-2.1	-2.0	-1.9
Weight Z-score; mean	-1.5	-1.2	-1.8	-1.3	-1.6	-1.2

Example 2. Primary Efficacy Endpoint

[00307] For this study, the primary estimand is the improvement in pruritus measured as change from baseline in the average morning ItchRO(Obs) severity score in the maralixibat treatment group relative to the placebo group. The primary analysis on the primary efficacy endpoint was conducted in 1) participants with PFIC 2 who fulfill criteria for the primary cohort in the ITT population (non-truncated primary "BSEP cohort" or "Primary cohort" with N = 31), 2) all PFIC participants (excluding the participants with prior history of surgery, heterozygous participants and unknown types, "All PFIC cohort" or "PFIC cohort" with N = 64), and 3) all study participants cohort, including the participants with prior history of surgery, heterozygous participants and unknown types. A restricted maximum likelihood (REML)-based mixed-effects model for repeated measures (MMRM) was used as the primary analysis method. The repeated measures includes post-baseline visits during the dose escalation phase (i.e., Week 6) and stable dosing phase (i.e., Weeks 10, 14, 18, 22, and 26), with change from baseline in the 6- or 4-week average morning ItchRO(Obs) severity score as the dependent variable. The MMRM model includes the fixed, categorical effects of treatment group, visit, and treatment group-by-visit interaction as well as the continuous, fixed covariates of baseline 4-week average morning ItchRO(Obs) severity score and the baseline score-by-visit interaction.

[00308] The primary efficacy analysis compared maralixibat and placebo using the contrast (difference in least squares [LS] means) between treatment groups across the last 12 weeks of the

Table 7. TEAEs of Clinical Interest Occurring in ≥5% of Participants in Either Arm, by FMQ and Preferred Term

TEAE, n (%)	MRX (n=47)	Placebo (n=46)
Gastrointestinal		
Diarrhoea	27 (57.4)	9 (19.6)
Abdominal pain	12 (25.5)	6(13)
Constipation	4(8.5)	2(4.3)
Gastroenteritis	3 (6.4)	2 (4.3)
Haematochezia	3 (6.4)	11 (2.2)
Vomiting	3 (6.4)	5 (10.9)
Liver function tests		
Transaminase AEs	8(17)	3 (6.5)
Increased ALT	6(12.8)	3(6.5)
Hyperbilirubinemia	7(14.9)	9(19.6)
FSV deficiency	13 (27.7)	16 (34.8)
Fractures	3 (6.4)	0

[00342] Transaminase adverse events (AEs) were observed in 17% and 6.5% of MRX and PBO patients, respectively (**Table 7**). Among the 8 participants receiving MRX who had transaminase elevations, 6 had resolution of the elevation without drug interruption; 2 patients had ongoing stable elevation even after drug interruption (n=1) or dose reduction (n=1), and both ultimately resumed prior maximum dose. No patients discontinued MRX due to transaminase elevation.

[00343] There was no evidence to suggest that MRX treatment contributes to Fat Soluble Vitamin (FSV) deficiency. FSV deficiency, which was reported as an AE, was also less common in MRX vs PBO (27.7% vs 34.8%). No clinically meaningful changes from baseline in setrum levels of vitamins A, D, and E were observed in the study population under regular FSV supplementation due to chronic cholestasis. Bilirubin increase was less common in MRX vs PBO (14.9% vs 19.6%). International normalized ratio (INR) decreased (improved) at every timepoint assessed with a mean change from Baseline of -0.3 for MRX vs -0.03 for placebo at week 26.

[00344] Fractures were seen in 6.4% of MRX and in 0% of PBO; none were considered treatment related as all had clear alternative causes for fracture, including pre-existing vitamin D deficiency which was stable or improved on MRX. Serious AEs were reportedin 10.6% of MRX

[00354] **Results:** 64 patients (nt-BSEP [n=31], FIC1 [n=13], MDR3 [n=9], TJP2 [n=7], and MYO5B [n=4]) were randomized to MRX (n=33) or PBO (n=31). Baseline characteristics were well-balanced between treatment arms (**Table 9**). Baseline pruritus score (ItchRO[Obs]) was 2.9 vs 2.7 for MRX and PBO. From Baseline to Week 26, the proportion (SE) of pruritus assessments ≤1 was greater in MRX (0.62 [0.06]) vs PBO (0.27 [0.06]) groups and the difference was significant (delta [95% CI]: 0.35 [0.19, 0.50]) (**Fig. 27B**). From Weeks 15-26, the median proportion of reported days with an ItchRO(Obs) score of 0-1 was 95% for MRX and 9% for PBO (p=0.0005). Pruritus response from Weeks 15-26 using ItchRO(Obs) was greater in the MRX group when measured in the morning (delta [95% CI]: -1.20 [-1.73, -0.67]), evening (delta: -1.16 [-1.69, -0.63]), or max daily (delta: -1.20 [-1.74, -0.66]) (**Fig. 27C**). Pruritus response measured with the CSS was greater in MRX (delta: -1.8 [-2.2, -1.53]) vs PBO (delta: -0.7 [-1.1, -0.3]) groups and the difference was significant (delta: -1.1 [-1.7, -0.6]; p< 0.0002). The CFB in sleep was greater in MRX (delta: -1.74 [-2.15, -1.33]) vs PBO (delta: -0.55 [-0.99, -0.11]) groups and the difference was significant (delta:-1.19 [-1.78, -0.60]; p=0.0002) (**Fig. 27D**). Throughout the study, there was a strong correlation between absolute values in pruritus and sleep scores (Spearman's r=0.93; p<0.0001) and also between change for Baseline for pruritus and sleep (Spearman's r=0.93; p<0.0001) (**Fig. 27E**).

Table 9. Baseline Characteristics Between Treatment Arms

Variable	Maralixibat (n = 33)	Placebo (n = 31)
Age, years	4.9	4.4
Male, %	52	42
Pruritus, ItchRO(Obs) score	2.85	2.73
Baseline CSS score	2.8	2.6
Baseline EDQ(Obs) sleep disturbance	3.70	3.66
Total sBA, pmol/L	254	272
UDCA usage, %	82	97
Rifampicin usage, %	55	48
Alanine aminotransferase, U/L	88	127
Total bilirubin, mg/dL	4.12	4.04
Direct bilirubin, mg/dL	2.98	2.93
Height Z-score	-2.08	-2.06
Weight Z-score	-1.75	-1.28

All data are mean unless otherwise indicated. Percentages aer 100 x n/N. UDCA is urodeoxycholic acid.

[00355] **Conclusions:** MRX was associated with complete or near-complete resolution of pruritus in the majority of patients with PFIC, and the effect was independent of how it was measured, or who made the assessments. Changes with pruritus were strongly correlated with changes in sleep, suggesting that use of MRX may yield meaningful improvements in this domain of quality of life.

Example 9. Long-Term Maintenance of Response and Improved Liver Health with Maralixibat in Patients with Progressive Familial Intrahepatic Cholestasis (PFIC)

[00356] Eighty-five patients from MARCH trial enrolled in MARCH-ON (**Table 10**, **Fig. 29A**). Fourty-seven patients had received Maralixibat (MRX-MRX) and 38 had received placebo (PBO-MRX) during MARCH trial.

Table 10. Baseline Characteristics Between Treatment Arms

Variable	MRX-MRX (n = 47)	PBO-MRX (n = 38)
Age, years	4.8	5.1
Male, %	43	42
Pruritus, ItchRO(Obs) score	2.8	2.5
Total sBA, pmol/L	263	253
UDCA usage, %	83	82
Rifampicin usage, %	55	58
Alanine aminotransferase, U/L	108	102
Total bilirubin, pmol/L	70	77
Direct bilirubin, pmol/L	51	57
Height Z-score	-1.9	-2.0
Weight Z-score	-1.5	-1.2

All data are mean unless otherwise indicated. Percentages aer 100 x n/N. UDCA is urodeoxycholic acid.

[00357] PFIC subtypes of patients included in the study were: non-truncated bile salt export pump (nt-BSEP, n=27), familial intrahepatic cholestasis-associated protein type 1 (F1C1, n=13); multidrug-resistance 3 protein (MDR3, n=9); tight junction protein 2 (TJP2, n=6); myosin VB (MYO5B, n=2); heterozygosis (n=2); truncated BSEP (t-BSEP, n=9); variant not found (n=8), fluctuating sBA (n=2); and surgery (n=7). Efficacy analyses included n = 33 in the MRX-MRX group and n= 24 in the PRO-MRX griup. Subtypes nt-BSEP, F1C1, MDR3, TJP2, and MYO5B were included in the efficacy analyses. Baseline was defined as the start of maralixibat (MRX) treatment for each group.

[00358] **Methods**: Long-term maintenance of response was assessed for patients who were originally randomized to receive MRX in MARCH and continued with treatment in MARCH-ON (MRX-MRX group; n=33). MRX response was assessed for patients who received PBO in the MARCH study and switched to open-label MRX in MARCH-ON (PBO-MRX group; n=24). Assessments included: pruritus measured by 0-4 scale of ItchRO[Obs], sBA, bilirubin, and growth z-scores, as well as incidence of treatment-emergent adverse events(TEAEs). Baseline (BL) was defined as the start of MRX for each group.

[00359] **Results:** For the MRX-MRX group, the median (min, max) time on MRX was 394 days (108, 836). In total, 20 of 33 patients reached Week 52 at time of analysis. Significant improvements observed in the first 26 weeks of the MARCH study were sustained from Baseline (BL) through Week 52 in MARCH-ON for pruritus severity (-2.17, p<0.0001), sBA (-200 µmol/L, p=0.0004), bilirubin (-2.64 mg/dL, p=0.0084), height z-score (+0.54, p<0.0001), and weight z-score (+0.44, p=0.0010) (**Fig. 29B-C**, **Table 11**). In the PBO-MRX group, the median time on MRX was 256 days (29,569). In total, 15 of 24 patients reached Week 26 at time of analysis. Newly gained statistically significant reductions in pruritus and sBA levels were observed in the key efficacy end points from BL through Week 26 for pruritus (-1.05, p=0.0017) and sBA (-141 µmol/L, p=0.0003) (**Fig. 29D-E**, **Table 11**), in line with observations from the initial MARCH MRX group. Overall, there were no new safety signals identified (**Table 12**). The most frequent TEAEs were gastrointestinal (GI)-related with early onset of diarrhea (51%) in line with the mechanism of IBAT inhibition, mostly mild and transient. In the MRX-MRX sub-group, fewer patients experienced diarrhea in MARCH-ON supporting these effects are early and transient in nature.

Table 11. Significant Improvements in Key Endpoints were Observed from Baseline to Week 52 in the MRX-MRX group and Basemine to Week 26 in the PBO-MRX group

Mean change from Baseline	MRXMRX (n = 20)[a]	PBO-MRX (n = 15)[b]
Pruritus. ltchR0(Obs) score	-2.17 (p< 0.0001)	-1.05 (p = 0.0017)
sBA, µmol/L	-200 (p = 0.0004)	-141 (p = 0.0003)
Total bilirubin, µmol/dL	-45 (p = 0.0084)	-27 (p = 0.1878)
Height Z-score	+0.54 (p< 0.0001)	+0.46 (p = 0.0152}
Weight Z-score	+0.44 (p = 0.00101)	+0.00 (p = 0.5134)

[a]Analysis includes n=20 patients in the MRX-MRX group with follow-up to Week 52.

[b]Analysis includes n=15 patients in the PBO-MRX group with follow-up to Week 26.

Table 12. No New Safety Signals were Identifies During Treatment with Maralixibat

TEAEs, n(%)	MRX-MRX (n = 47)	PBO-MRX (n = 38)
Any TEAE	47 (1M)	35 (92.1)
Severe TEAE	5 (10.6)	2 (5.3)
Serious TEAE	8 (17.0)	6 (15.0)
TEAE leading to discontinuation	3 (6.4)	0
TEAE leading to death	1 (2-1)	0
Most common TEAE: diarrhoea	30 (63.8)	13 (34.2)

Percentages are 100 x n/N. TEAE is treatment-emergent adverse effect.

[00360] Conclusions: Significant and sustained responses in pruritus, sBA, bilirubin as well as growth are observed with 52 weeks of MRX treatment across the broadest range of genetic PFIC types studied to date. The PBO-MRX group demonstrated significant improvements in pruritus severity and sBA levels similar to those observed in the original MARCH maralixibat group. These data suggest overall improved liver health with MRX treatment which can be maintained over time.

Example 10. Impact of Maralixibat (MRX) on Cholestatic Pruritus in Adults Aged 16 Years and Older with Alagille Syndrome (ALGS)

[00361] The efficacy and safety of MRX in participants with ALGS aged ≥16 years transitionig to adult care and participant aged >16 years who initiate MRX treatment were studied (**Fig. 30**). The median (min, max) duration of therapy for participants who initiated MRX at <16 years of age was 4.1 years (1.5, 5.9), with the oldest patient taking MRX at 21 years of age (**Table 13**). Three participants began MRX at ≥16 years of age and were followed for a median of 3.8 years.

Table 13. Key Demographics and Baseline Characteristics (N=14)

Variable **Mean (SE)** **Unless specified**	**Participants <16 y at MRX initiation (n=11)**	**Participants >16 y at MRX initiation (n=3)**
Age, y	13.2 (0.4)	16.3 (0.3)
Sex, male, %	45.5	66.7
Pruritus, ItchRO(Obs)	2.5 (0.2)	3.1 (0.4)
Total sBA, µmol/L	130 (39)	82 (57)
Total bilirubin, mg/dL	36.4 (12.6)	27.9 (14.3)
Direct bilirubin, mg/dL	28.1 (11.5)	17.7 (10.0)
Height z score	-1.8 (0.5)	-1.0 (0.3)
Weight z score	-1.8 (0.3)	-1.1 (0.4)
ALT, U/L	174 (52)	106 (12)

[00362] ALT is alanine aminotransferase. Adverse events (AEs) decreased as patients got older (**Table 14**).

Table 14. Summary of treatment-emerged adverse effects (TEAEs) in full study cohort (N=14).

TEAE, n (%)	**Participants aged <16 y at MRX initiation (n=11)[a]**		**Participants aged >16 y at MRX initiation (n=3)**
	Before 16 y	**After 16 y**	
Any TEAEs	11 (100)	7 (63.6)	3(100)
TEAEs > grade 3	1 (9.1)	1 (9.1)	1 (33.3)
Treatment-related AEs	9 (81.8)	2 (18.2)	2 (66.7)
Treatment-related AEs ≥grade 3[b]	0	0	1 (33.3)
SAEs	2 (18.2)	1 (9.1)	0
Treatment-related SAEs	0	0	0
AEs leading to study drug discontinuation	0	0	0
AEs leading to study discontinuation	0	0	0
AEs leading to death **Gastrointestinal TEAEs**	0	0	0
Diarrhoea	6 (54.5)	1 (9.1)	1 (33.3)
Abdominal pain	5 (45.5)	2 (18.2)	0

Participant ID	Treatment	Timepoint	sBA (µmol/L)			Total Bilirubin (mg/dL)			ALT (U/L)		
			Value	Chg from BL	% Chg from BL	Value	Chg from BL	% Chg from BL	Value	Chg from BL	% Chg from BL
008-001	MRX-MRX	Baseline	265			1.15			123		
		Week 26	364	+99	+37.4%	0.9	-0.25	-21.7%	118	-5	-4.1%
		Week 58	208	-57	-21.5%	0.8	-0.35	-30.4%	116	-7	-5.7%
033-006	MRX-MRX	Baseline	516			3.85			320		
		Week 26	388	-128	-24.8%	2.6	-1.25	-32.5%	183	-127	-42.8%
		Week 58	48.6	-467.4	-90.6%	0.9	-2.95	-76.6%	28	-292	-91.3%
033-010	MRX-MRX	Baseline	453			2.25			381		
		Week 26	408	-45	-9.9%	3.10	+0.85	+37.8%	439	+58	+15.2%
		Week 58	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
038-003	MRX-MRX	Baseline	389			0.9			43		
		Week 26	314	-75	-19.3%	0.7	-0.2	-22.2%	44	+1	+2.3%
		Week 58	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
016-003	PBO-MRX	Baseline	410			3.95			297		
		Week 26	588	+178	+43.4%	5.3	+1.35	+34.2%	254	-43	-14.5%
		Week 52[a]	222	-366	-62.2%	1.2	-4.1	-77.4%	195	-59	-23.2%
023-002	PBO-MRX	Baseline	157			1.1			76		
		Week 26	282	+125	+79.6%	1.4	+0.3	+27.3%	92	+16	+21.1%
		Week 52[a]	349	+67	+23.8%	1.0	-0.4	-28.6%	170	+78	+84.8%
035-004	PBO-MRX	Baseline	234			3.25			136		
		Week 26	236	+2	+0.9%	5.0	+ 1.75	+53.8%	87	-49	-36.0%
		Week 52[a]	216	-20	-8.5%	7.7	+2.7	+54.0%	274	+ 187	+214.9%
043-001	PBO-MRX	Baseline	434			2.65			323		
		Week 26[b]	42/	-7	-1.6%	1.55	-1.1	-41.5%	234	-89	-27.6%
		Week 52[a,c]	309	-118	-27.6%	1.7	+0.15	+9.7%	345	+111	+47 4%

[a] Week 52 values are Week 26 values from study MRX-503 (representing 26 weeks of MRX treatment). The (present) change from baseline is calculated relative to the Week 26 result from study MRX-502.
[b] For Participant 043-001, Week 26 results were not available so the baseline value from MRX-503 was used instead.
[c] Week 22 results from Study MRX-503 were used.

[00370] This finding is highly surprising and unexpected given the predicted loss of function associated with this genotype.

[00371] All references cited anywhere within this specification are incorporated herein by reference in their entirety for all purposes.

[00372] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only.

[00373] Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range and each endpoint, unless otherwise indicated herein, and each separate value and endpoint is incorporated into the specification as if it were individually recited herein.

[00374] Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

WHAT IS CLAIMED IS:

1. Use of maralixibat, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a progressive familial intrahepatic cholestasis (PFIC) in a subject in need thereof, wherein the maralixibat or pharmaceutically acceptable salt thereof is to be administered in an amount from about 600 µg/kg/day to about 1400 µg/kg/day.

2. The use of claim 1, wherein the pharmaceutically acceptable salt of maralixibat is maralixibat chloride.

3. The use of any one of claims 1-2, wherein the maralixibat or pharmaceutically acceptable salt thereof is maralixibat chloride, and maralixibat chloride is to be administered in an amount of about 1200 µg/kg/day.

4. The use of any one of claims 1-3, wherein the PFIC is PFIC 1, PFIC 2, PFIC 3, PFIC 4, PFIC 5, or PFIC 6.

5. The use of claim 4, wherein the PFIC is PFIC 4, PFIC5 or PFIC6.

6. The use of any one of claims 1-5, wherein the PFIC is heterozygous.

7. The use of any one of claims 1-6, wherein the subject has intermittent cholestasis and/or the subject has undergone biliary diversion surgery.

8. The use of any one of claims 1-7, wherein the subject is a pediatric subject.

9. The use of any one of claims 1-8, wherein the subject has a mutation in a gene selected from the group consisting of: *ATP8B1*, *ABCB11*, *ABCB4*, *TJP2*, *NR1H4*, *MYO5B*, or a mutation that is not a known or identified pathogenic variant.

10. The use of any one of claims 1-8, wherein the mutation is a non-truncating mutation.

11. The use of any one of claims 1-8, wherein the mutation is a truncating mutation in a BSEP protein.

12. The use of any one of claims 1-9, wherein the maralixibat or pharmaceutically acceptable salt thereof is to be administered once daily (QD) or twice daily (BID).

13. The use of any one of claims 1-12, wherein the maralixibat or pharmaceutically acceptable salt thereof is maralixibat chloride, and maralixibat chloride is to be administered at 600 µg/kg/day BID for a total daily dose of 1200 µg/kg/day.

14. The use of any one of claims 1-13, further comprising a lipid soluble vitamin (LSV) to be administered in subjects with LSV deficiency, preferably wherein the LSV is selected from the group consisting of Vitamin A, Vitamin D and Vitamin E.

15. The use of any one of claims 1-14, wherein the maralixibat or pharmaceutically acceptable salt thereof is to be administered BID, about 30 minutes before the morning meal and about 30 minutes before the evening meal.

16. Use of a pharmaceutical composition comprising maralixibat, or a pharmaceutically acceptable salt thereof, an antioxidant, and a preservative in the manufacture of a medicament for treating a progressive familial intrahepatic cholestasis (PFIC) in a subject in need thereof.

17. The use of claim 16, wherein the pharmaceutical composition is a liquid composition to be administered orally, and wherein the preservative is an antimicrobial preservative selected from the group consisting of propylene glycol, ethyl alcohol, glycerin, benzalkonium chloride, benzethonium chloride, benzoic acid, benzyl alcohol, butylparaben, cetrimide (cetyltrimethylammonium bromide), cetrimonium bromide, cetylpyridinium chloride, chlorhexidine, chlorobutanol, chlorocresol, cresol, ethylparaben, methylparaben, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric acetate, phenylmercuric borate, phenylmercuric nitrate, propylparaben, sodium benzoate, sodium dehydroacetate, sodium propionate, sorbic acid, potassium sorbate, thimerosal, thymol, and combinations thereof, and wherein the antioxidant is an aminopolycarboxylic acid selected from EDTA (ethylenediaminetetraacetic acid), DTPA (diethylenetriaminepentaacetic acid), EGTA (ethylene glycol-bis(β-aminoethyl ether)-N,N,N′,N′-tetraacetic acid), NTA (nitrilotriacetic acid), BAPTA (1,2-bis(o-aminophenoxy)ethane-N,N,N′,N′-tetraacetic acid), NOTA (2,2',2"-(1,4,7-triazonane-1,4,7-triyl)triacetic acid), DOTA (tetracarboxylic acid), and EDDHA (ethylenediamine-N,N′-bis(2-hydroxyphenylacetic acid)..

18. The use of any one of claims 16-17, wherein the pharmaceutical composition comprises:

a. from about 8 mg/mL to about 20 mg/mL of maralixibat;

b. from about 330 mg/mL to about 380 mg/mL of propylene glycol;
c. about 1 mg/mL of disodium EDTA;
d. a sweetener, a taste-masking ingredient, or a combination thereof, and
e. water.