[0004] Pediatric cholestatic liver diseases affect a small percentage of children, but therapy results in significant healthcare costs each year. Currently, many of the pediatric cholestatic liver diseases require invasive and costly treatments such as liver transplantation and surgery.

[0005] It is well understood and accepted that the therapeutic needs of children are sufficiently different than those of adults as to require specific studies of medications in children. For example, oral administration of a solid dosage form of medication is painless and simple for most adult patients, but for the pediatric patient population, swallowing an oral solid dosage form produced for adults can be problematic. In addition, the drugs used in solid dosages often have an unpleasant taste. More importantly, oral administration of adult medication targeting cholestatic liver diseases may result in side effects such as diarrhea and intestinal discomfort. Such problems pose a safety risk and affect compliance. Effective and acceptable forms of pediatric medication for pediatric cholestatic liver diseases are needed.

[0006] The apical sodium-dependent transporter (ASBT) protein located in the terminal ileum plays an important physiological role in the enterohepatic circulation of bile acids and therefore essential for the bile acid homeostasis. To this end, pharmacological inhibition of ASBT is fast emerging as an interesting target.

[0007] Some ASBT inhibitors (ASBTIs) are designed to limit systemic absorption by the individual. In this regard, in some cases formulating these compounds into stable and effective compositions may be challenging.

[0008] Thus, there exists an unmet need for safe and effective formulations and compositions comprising ASBTIs.

SUMMARY OF THE DISCLOSURE

[0009] Various non-limiting examples of the disclosureare described below.

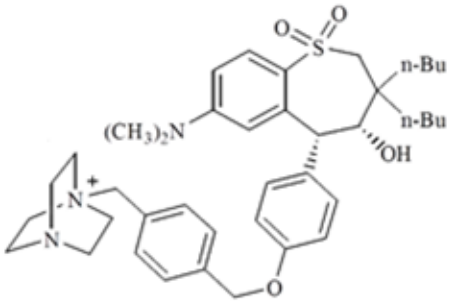
[00010] In one aspect, the present disclosureprovides a pharmaceutical composition comprising an ASBTI, a preservative, and an antioxidant.

[00011] In one example, the preservative is an antimicrobial preservative. In one example, the preservative is propylene glycol.

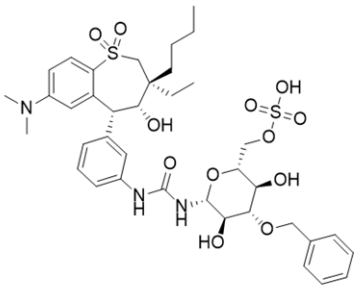
[00012] In one example, the preservative is present in an amount of at least 30% of the composition. In one example, the preservative is present in an amount of from about 30% to about 40% of the composition. In one example, the preservative is present in an amount of from about 32% to about 37% of the composition. In one example, the preservative is present in an amount of from about 33% to about 36% of the composition. In one example, the preservative is present in an amount of about 33% of the composition. In one example, the preservative is present in an amount of about 34% of the composition. In one example, the preservative is present in an amount of about 35% of the composition.

[00013] In one example, the antioxidant is an aminocarboxylic acid or an aminopolycarboxylic acid. 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.

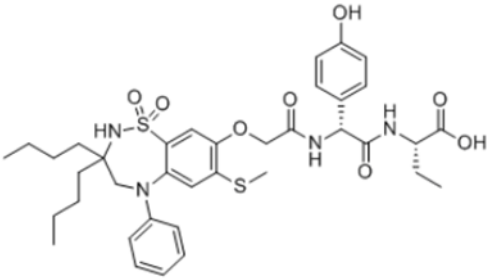
[00014] In one example, the ASBTI is



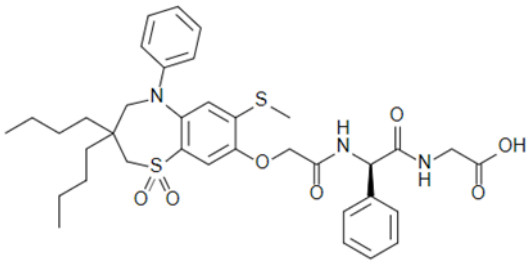
(maralixibat),



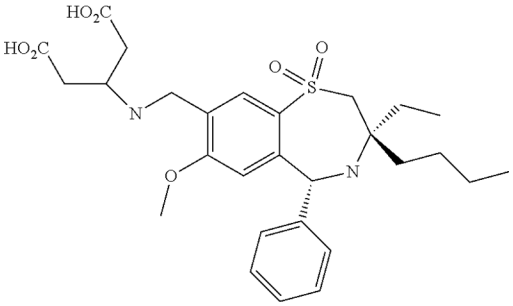
(volixibat),



(odevixibat),

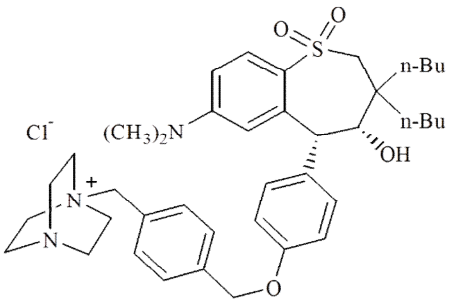


(elobixibat),



(GSK2330672), or a pharmaceutically acceptable salt thereof.

[00015] In one example, the ASBTI is



(maralixibat chloride).

[00016] In one example, the ASBTI is volixibat, or a pharmaceutically acceptable salt thereof.

[00017] In one example, the ASBTI is odevixibat, or a pharmaceutically acceptable salt thereof.

[00018] In one example, the ASBTI is elobixibat, or a pharmaceutically acceptable salt thereof.

[00019] In one example, the ASBTI is GSK2330672, or a pharmaceutically acceptable salt thereof.

[00020] In one example, the ASBTI is present in an amount of about 0.1 mg/mL to about 500 mg/mL of the composition. In one example, the ASBTI is present in an amount of about 1 mg/mL to about 250 mg/mL of the composition. In one example, the ASBTI is present in an amount of about 2 mg/mL to about 100 mg/mL of the composition. In one example, the ASBTI is present in an amount of about 5 mg/mL to about 50 mg/mL of the composition. In one example, the ASBTI is present in an amount of about 8 mg/mL to about 20 mg/mL of the composition. In one example, the ASBTI is present in an amount of about 9 mg/mL to about 10 mg/mL of the composition. In one example, the ASBTI is present in an amount of about 10 mg/mL of the composition. In one example, the ASBTI is present in an amount of about 9.5 mg/mL of the composition.

[00021] In one example, the preservative is an antimicrobial preservative.

[00022] 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.

[00023] In one example, the preservative is propylene glycol.

[00024] In one example, the preservative is present in an amount of at least about 30% w/w of the composition. In one example, the preservative is present in an amount of from about 30% to about 40% of the composition. In one example, the preservative is present in an amount of from about 32% to about 37% of the composition. In one example, the preservative is present in an amount of from about 33% to about 36% of the composition. In one example, the preservative is present in an amount of about 33% of the composition. In one example, the preservative is present in an amount of about 34% of the composition. In one example, the preservative is present in an amount of about 35% of the composition.

[00025] 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.

[00026] 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)

[00027] In one example, the antioxidant is EDTA.

[00028] In one example, the antioxidant is present in an amount of about 0.001% to about 1% w/w of the composition. In one example, the antioxidant is present in an amount of about 0.005% to about 0.75% w/w of the composition. In one example, the antioxidant is present in an amount of about 0.01% to about 0.5% w/w of the composition. In one example,

the antioxidant is present in an amount of about 0.05% to about 0.25% w/w of the composition. In one example, the antioxidant is present in an amount of about 0.075% to about 0.2% w/w of the composition. In one example, the antioxidant is present in an amount of about 0.1% w/w of the composition.

[00029] In one example, the composition is stable for at least 1 month at room temperature. In one example, the composition is stable for at least 2 months at room temperature. In one example, the composition is stable for at least 3 months at room temperature. In one example, the composition is stable for at least 6 months at room temperature. In one example, the composition is stable for at least 1 year at room temperature. In one example, the composition is stable for at least 2 years at room temperature.

[00030] In one example, the composition is a liquid composition for oral administration. In one example, the composition is an aqueous solution.

[00031] In one example, the composition further comprises a sweetener, a taste-masking ingredient, or a combination thereof.

[00032] In another aspect, the present disclosureprovides a pharmaceutical composition comprising:

a. from about 5 mg/mL to about 50 mg/mL of maralixibat;
b. from about 300 mg/mL to about 400 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.

[00033] 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.

[00034] In one example, maralixibat is present as maralixibat chloride.

[00035] In one example, the pharmaceutical composition further comprises a second therapeutic agent.

[00036] In one example, the second therapeutic agent is ursodeoxycholic acid (UDCA), rifampicin, an antihistamine, or an FXR-targeting drug.

[00037] In another aspect, the present disclosureprovides a pharmaceutical dosage form for oral administration comprising the pharmaceutical composition as described herein.

[00037a] In another aspect, the present disclosure provides a use of the pharmaceutical composition as described herein or the pharmaceutical dosage form as described herein in the manufacture of a medicament for treating or ameliorating a pediatric cholestatic liver disease in a pediatric subject.

[00038] In another example, the present disclosureprovides a method of treating or ameliorating a pediatric cholestatic liver disease comprising administering to a pediatric subject a therapeutically effective amount of the pharmaceutical composition or the pharmaceutical dosage form of any of the preceding examples.

[00039] In one example, the pediatric cholestatic liver disease is progressive familial intrahepatic cholestasis (PFIC), PFIC type 1, PFIC type 2, PFIC type 3, Alagille syndrome (ALGS), biliary atresia (BA), post-Kasai biliary atresia, post-liver transplantation biliary atresia, Dubin-Johnson Syndrome, post-liver transplantation cholestasis, post-liver transplantation associated liver disease, intestinal failure associated liver disease, bile acid mediated liver injury, pediatric primary sclerosing cholangitis (PSC), MRP2 deficiency syndrome, neonatal sclerosing cholangitis, a pediatric obstructive cholestasis, a pediatric non-obstructive cholestasis, a pediatric extrahepatic cholestasis, a pediatric intrahepatic cholestasis, a pediatric primary intrahepatic cholestasis, a pediatric secondary intrahepatic cholestasis, benign recurrent intrahepatic cholestasis (BRIC), BRIC type 1, BRIC type 2, BRIC type 3, total parenteral nutrition associated cholestasis, paraneoplastic cholestasis, Stauffer syndrome, drug-associated cholestasis, infection-associated cholestasis, or gallstone disease.

[00040] In one example, the pediatric cholestatic liver disease is PFIC, ALGS, BA, or pediatric PSC.

[00041] In one example, the pediatric cholestatic liver disease is characterized by one or more symptoms selected from jaundice, pruritus, cirrhosis, hypercholemia, neonatal respiratory distress syndrome, lung pneumonia, increased serum concentration of bile acids, increased hepatic concentration of bile acids, increased serum concentration of bilirubin, hepatocellular injury, liver

scarring, liver failure, hepatomegaly, xanthomas, malabsorption, splenomegaly, diarrhea, pancreatitis, hepatocellular necrosis, giant cell formation, hepatocellular carcinoma, gastrointestinal bleeding, portal hypertension, hearing loss, fatigue, loss of appetite, anorexia, peculiar smell, dark urine, light stools, steatorrhea, failure to thrive, and renal failure.

[00041a] In another aspect, the present disclosure provides a use of the pharmaceutical composition as defined herein or the pharmaceutical dosage form as defined herein in the manufacture of a medicament for treating or ameliorating pruritus in a pediatric subject.

[00042] In another example, the present disclosureprovides a method of treating or ameliorating pruritus comprising administering to a pediatric subject a therapeutically effective amount of the pharmaceutical composition or the pharmaceutical dosage form of any of the preceding examples.

[00042a] In another aspect, the present disclosure provides a use of the pharmaceutical composition as described herein or the pharmaceutical dosage form as described herein in the manufacture of a medicament for treating or ameliorating hypercholemia in a pediatric subject.

[00043] In another example, the present disclosureprovides a method of treating or ameliorating hypercholemia comprising administering to a pediatric subject a therapeutically effective amount of the pharmaceutical composition or the pharmaceutical dosage form of any of the preceding examples.

[00043a] In another aspect, the present disclosure provides a use of the pharmaceutical composition as described herein or the pharmaceutical dosage form as described herein in the manufacture of a medicament for treating or ameliorating xanthoma in a pediatric subject.

[00044] In another example, the present disclosureprovides a method of treating or ameliorating xanthoma comprising administering to a pediatric subject a therapeutically effective amount of the pharmaceutical composition or the pharmaceutical dosage form of any of the preceding examples.

[00044a] In another aspect, the present disclosure provides a use of the pharmaceutical composition as described herein or the pharmaceutical dosage form as described herein in the manufacture of a medicament for decreasing the level of serum or hepatic bile levels in a pediatric subject.

[00045] In another example, the present disclosureprovides a method of decreasing the level of serum or hepatic bile levels in a subject comprising administering to a

pediatric subject a therapeutically effective amount of the pharmaceutical composition or the pharmaceutical dosage form of any of the preceding examples.

[00046] In one exampleof any of the preceding methods, the pediatric subject is between 6 months and 18 years of age.

[00047] In one exampleof any of the preceding methods, the method further comprises administering a second therapeutic agent.

[00048] In one example, the second therapeutic agent is UDCA, rifampicin, an antihistamine, an FXR-targeting drug, or a combination thereof.

[00049] In one example, the second therapeutic agent is administered in a subclinical therapeutically effective amount.

[00050] In yet another example, the present disclosureprovides a method of treating or ameliorating a pediatric cholestatic liver disease comprising administering to a pediatric subject a therapeutically effective amount of the pharmaceutical composition or the pharmaceutical dosage form of any of the preceding examplesin combination with a subclinical therapeutically effective amount of a second therapeutic agent selected from the group consisting of UDCA, rifampicin, an antihistamine, and an FXR-targeting drug.

[00050a] In another aspect, the present disclosure provides a use of the pharmaceutical composition as described herein or the pharmaceutical dosage form as described herein in combination with a subclinical therapeutically effective amount of a second therapeutic agent selected from the group consisting of UDCA, rifampicin, an antihistamine, an FXR-targeting drug, and a PPAR agonist in the manufacture of a medicament for treating or ameliorating a pediatric cholestatic liver disease.

[00051] In one example, the subclinical therapeutically effective amount of the second therapeutic agent is at least 10% lower than the amount of the second therapeutic agent administered as a monotherapy. In one example, the subclinical therapeutically effective amount of the second therapeutic agent is at least 20% than the amount of the second therapeutic agent administered a monotherapy.

[00052] In one example, the second therapeutic agent is a PPAR agonist. In one example, the PPAR agonist is selected from bezafibrate, seladelpar (MBX-8025), GW501516 (Cardarine), fenofibrate, elafibranor, REN001, KD3010, ASP0367, and CER-002.

[00053] In one example, the PPAR agonist is a PPARδ agonist. In one example, the PPARδ agonist is selected from seladelpar (MBX-8025), REN001, KD3010, ASP0367, and CER-002.

[00054] In yet another example, the present disclosureprovides a method of treating or ameliorating a pediatric cholestatic liver disease comprising administering to a pediatric subject a therapeutically effective amount of maralixibat in combination with a therapeutically effective amount of a PPAR agonist.

[00054a] In another aspect, the present disclosure provides a use of maralixibat in combination with a PPAR agonist in the manufacture of a medicament for treating or ameliorating a pediatric cholestatic liver disease.

[00055] In one example, the PPAR agonist is selected from bezafibrate, seladelpar (MBX-8025), GW501516 (Cardarine), fenofibrate, elafibranor, REN001, KD3010, ASP0367, and CER-002.

[00056] In one example, the PPAR agonist is a PPARδ agonist. In one example, the PPARδ agonist is selected from seladelpar (MBX-8025), REN001, KD3010, ASP0367, and CER-002.

[00057] The method of claim 69, wherein the pediatric cholestatic liver disease is sclerosing cholangitis.

[00058] The method of claim 69, wherein the pediatric cholestatic liver disease is selected from PSC and PBC.

[00059] These and other examples of the present disclosurewill 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

[00060] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[00061] **Figure 1** is a plot of the stability of a maralixibat oral solution at 25° C and 60% relative humidity (RH).

[00062] **Figure 2** is a plot of the effect of Disodium EDTA Dihydrate concentration on oxidative impurity desmethyl maralixibat chloride Levels in a maralixibat oral solution at 25°C and 40°C.

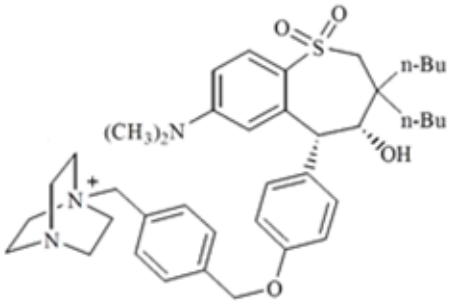
[00063] **Figures 3A-3E** are plots of ItchRO and doses of maralixibat and selected antipruritic medications for 5 exemplary PFIC patients enrolled in the LUM001-501 Study. **Figure 3A** shows the patient discontinued Rifampicin and UDCA while maintaining excellent pruritus control. **Figure 3B** shows the patient discontinued Rifampicin while maintaining excellent pruritus control. **Figure 3C** shows the patient discontinued Rifampicin while maintaining excellent pruritus control. **Figure 3D** shows the patient discontinued UDCA while maintaining pruritus control. **Figure 3E** shows the patient discontinued UDCA while maintaining pruritus control.

[00064] **Figure 4** depicts mean liver and serum bile acid, ALT, total bilirubin, and ALP concentrations, displayed in relation to mean values in vehicle treated MDR2-/- mice. One-way-ANOVA was applied to determine differences between treatment groups vs “vehicle control” with ****$p<0.0001$, ***$p<0.001$, **$p<0.01$, *$p<0.05$.

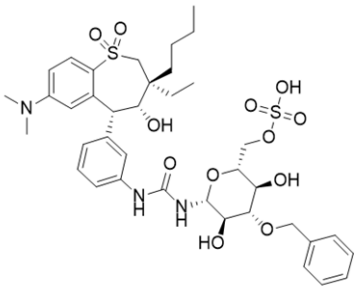
DETAILED DESCRIPTION

WHAT IS CLAIMED IS:

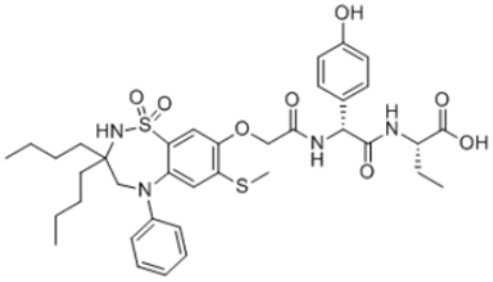
1. A pharmaceutical composition comprising an ASBTI, a preservative, and an antioxidant.
2. The pharmaceutical composition of claim 1, wherein the ASBTI is



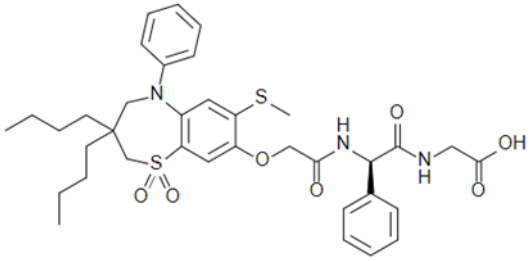
(maralixibat),



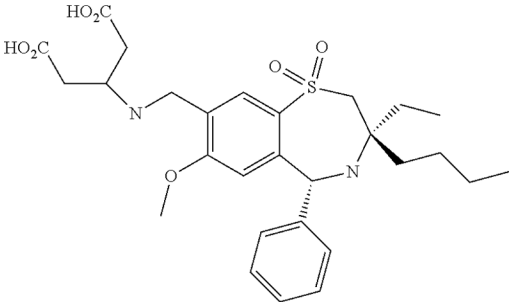
(volixibat),



(odevixibat),

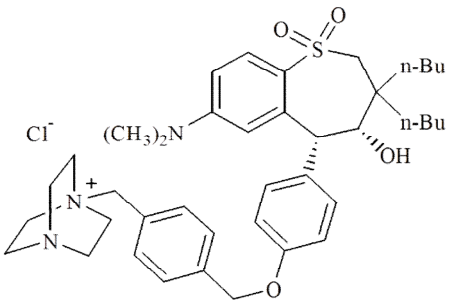


(elobixibat),



(GSK2330672), or a pharmaceutically acceptable salt thereof.

3. The pharmaceutical composition of claims 1 or 2, wherein the ASBTI is



(maralixibat chloride).

4. The pharmaceutical composition of claims 1 or 2, wherein the ASBTI is volixibat, or a pharmaceutically acceptable salt thereof.
5. The pharmaceutical composition of claims 1 or 2, wherein the ASBTI is odevixibat, or a pharmaceutically acceptable salt thereof.
6. The pharmaceutical composition of claims 1 or 2, wherein the ASBTI is elobixibat, or a pharmaceutically acceptable salt thereof.
7. The pharmaceutical composition of claims 1 or 2, the ASBTI is GSK2330672, or a pharmaceutically acceptable salt thereof.
8. The pharmaceutical composition of any of claims 1-7 wherein the ASBTI is present in an amount of about 0.1 mg/mL to about 500 mg/mL of the composition.
9. The pharmaceutical composition of any of claims 1-8 wherein the ASBTI is present in an amount of about 1 mg/mL to about 250 mg/mL of the composition.
10. The pharmaceutical composition of any of claims 1-9 wherein the ASBTI is present in an amount of about 2 mg/mL to about 100 mg/mL of the composition.
11. The pharmaceutical composition of any of claims 1-10 wherein the ASBTI is present in an amount of about 5 mg/mL to about 50 mg/mL of the composition.
12. The pharmaceutical composition of any of claims 1-11 wherein the ASBTI is present in an amount of about 8 mg/mL to about 20 mg/mL of the composition.
13. The pharmaceutical composition of any of claims 1-12 wherein the ASBTI is present in an amount of about 9 mg/mL to about 10 mg/mL of the composition.
14. The pharmaceutical composition of any of claims 1-13 wherein the preservative is an antimicrobial preservative.

15. The pharmaceutical composition of claim 14, wherein 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.
16. The pharmaceutical composition of any of claims 1-15, wherein the preservative is propylene glycol.
17. The pharmaceutical composition of any of claims 1-16, wherein the preservative is present in an amount of at least about 30% w/w of the composition.
18. The pharmaceutical composition of any of claims 1-17, wherein the preservative is present in an amount of from about 30% to about 40% of the composition.
19. The pharmaceutical composition of any of claims 1-18, wherein the preservative is present in an amount of from about 32% to about 37% of the composition.
20. The pharmaceutical composition of any of claims 1-19, wherein the preservative is present in an amount of from about 33% to about 36% of the composition.
21. The pharmaceutical composition of any of claims 1-20, wherein the preservative is present in an amount of about 33% of the composition.
22. The pharmaceutical composition of any of claims 1-20, wherein the preservative is present in an amount of about 34% of the composition.
23. The pharmaceutical composition of any of claims 1-20, wherein the preservative is present in an amount of about 35% of the composition.
24. The pharmaceutical composition of any of claims 1-23, wherein 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.

25. The pharmaceutical composition of any of claims 1-24, 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)
26. The pharmaceutical composition of any of claims 1-25, wherein the antioxidant is EDTA.
27. The pharmaceutical composition of any of claims 1-26, wherein the antioxidant is present in an amount of about 0.001% to about 1% w/w of the composition.
28. The pharmaceutical composition of any of claims 1-27, wherein the antioxidant is present in an amount of about 0.005% to about 0.75% w/w of the composition.
29. The pharmaceutical composition of any of claims 1-28, wherein the antioxidant is present in an amount of about 0.01% to about 0.5% w/w of the composition.
30. The pharmaceutical composition of any of claims 1-29, wherein the antioxidant is present in an amount of about 0.05% to about 0.25% w/w of the composition.
31. The pharmaceutical composition of any of claims 1-30, wherein the antioxidant is present in an amount of about 0.075% to about 0.2% w/w of the composition.
32. The pharmaceutical composition of any of claims 1-31, wherein the antioxidant is present in an amount of about 0.1% w/w of the composition.
33. The pharmaceutical composition of any of claims 1-32, wherein the composition is stable for at least 1 month at room temperature.
34. The pharmaceutical composition of any of claims 1-33, wherein the composition is stable for at least 2 months at room temperature.
35. The pharmaceutical composition of any of claims 1-34, wherein the composition is stable for at least 3 months at room temperature.

36. The pharmaceutical composition of any of claims 1-35, wherein the composition is stable for at least 6 months at room temperature.
37. The pharmaceutical composition of any of claims 1-35, wherein the composition is stable for at least 1 year at room temperature.
38. The pharmaceutical composition of any of claims 1-35, wherein the composition is stable for at least 2 years at room temperature.
39. The pharmaceutical composition of any of claims 1-38, wherein the composition is a liquid composition for oral administration.
40. The pharmaceutical composition of claim 38, wherein the composition is an aqueous solution.
41. The pharmaceutical composition of any of claims 1-40, further comprising a sweetener, a taste-masking ingredient, or a combination thereof.
42. A pharmaceutical composition comprising:
    a. from about 5 mg/mL to about 50 mg/mL of maralixibat;
    b. from about 300 mg/mL to about 400 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.
43. The pharmaceutical composition of claim 42, comprising:
    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.
44. The pharmaceutical composition of any of claims 1-43, wherein maralixibat is present as maralixibat chloride.
45. The pharmaceutical composition of any of claims 1-43, further comprising a second therapeutic agent.

46. The pharmaceutical composition of claim 44, wherein the second therapeutic agent is ursodeoxycholic acid (UDCA), rifampicin, an antihistamine, or an FXR-targeting drug.
47. A pharmaceutical dosage form for oral administration comprising the pharmaceutical composition of any of claims 1-46.
48. Use of the pharmaceutical composition of any of claims 1-46 or the pharmaceutical dosage form of claim 47 in the manufacture of a medicament for treating or ameliorating a pediatric cholestatic liver disease in a pediatric subject.
49. The use of claim 48, wherein the pediatric cholestatic liver disease is progressive familial intrahepatic cholestasis (PFIC), PFIC type 1, PFIC type 2, PFIC type 3, Alagille syndrome (ALGS), biliary atresia (BA), post-Kasai biliary atresia, post-liver transplantation biliary atresia, Dubin-Johnson Syndrome, post-liver transplantation cholestasis, post-liver transplantation associated liver disease, intestinal failure associated liver disease, bile acid mediated liver injury, pediatric primary sclerosing cholangitis (PSC), MRP2 deficiency syndrome, neonatal sclerosing cholangitis, a pediatric obstructive cholestasis, a pediatric non-obstructive cholestasis, a pediatric extrahepatic cholestasis, a pediatric intrahepatic cholestasis, a pediatric primary intrahepatic cholestasis, a pediatric secondary intrahepatic cholestasis, benign recurrent intrahepatic cholestasis (BRIC), BRIC type 1, BRIC type 2, BRIC type 3, total parenteral nutrition associated cholestasis, paraneoplastic cholestasis, Stauffer syndrome, drug-associated cholestasis, infection-associated cholestasis, or gallstone disease.
50. The use of claim 48 or claim 49, wherein the pediatric cholestatic liver disease is PFIC, ALGS, BA, or pediatric PSC.
51. The use of any of claims 48-50, wherein the pediatric cholestatic liver disease is characterized by one or more symptoms selected from jaundice, pruritus, cirrhosis, hypercholemia, neonatal respiratory distress syndrome, lung pneumonia, increased serum concentration of bile acids, increased hepatic concentration of bile acids, increased serum concentration of bilirubin, hepatocellular injury, liver scarring, liver failure, hepatomegaly, xanthomas, malabsorption, splenomegaly, diarrhea, pancreatitis, hepatocellular necrosis, giant cell formation, hepatocellular carcinoma, gastrointestinal bleeding, portal

hypertension, hearing loss, fatigue, loss of appetite, anorexia, peculiar smell, dark urine, light stools, steatorrhea, failure to thrive, and renal failure.

52. Use of the pharmaceutical composition of any of claims 1-46 or the pharmaceutical dosage form of claim 47 in the manufacture of a medicament for treating or ameliorating pruritus in a pediatric subject.
53. Use of the pharmaceutical composition of any of claims 1-46 or the pharmaceutical dosage form of claim 47 in the manufacture of a medicament for treating or ameliorating hypercholemia in a pediatric subject.
54. Use of the pharmaceutical composition of any of claims 1-46 or the pharmaceutical dosage form of claim 47 in the manufacture of a medicament for treating or ameliorating xanthoma in a pediatric subject.
55. Use of the pharmaceutical composition of any of claims 1-46 or the pharmaceutical dosage form of claim 47 in the manufacture of a medicament for decreasing the level of serum or hepatic bile levels in a pediatric subject.
56. The use of any of claims 48-55, wherein the pediatric subject is between 6 months and 18 years of age.
57. The use of any of claims 48-56, further comprising a second therapeutic agent to be administered.
58. The use of claim 57, wherein the second therapeutic agent is UDCA, rifampicin, an antihistamine, an FXR-targeting drug, a PPAR agonist, or a combination thereof.
59. The use of claim 57 or claim 58, wherein the second therapeutic agent is to be administered in a subclinical therapeutically effective amount.
60. Use of the pharmaceutical composition of any of claims 1-46 or the pharmaceutical dosage form of claim 47 in combination with a subclinical therapeutically effective amount of a second therapeutic agent selected from the group consisting of UDCA, rifampicin, an antihistamine, an FXR-targeting drug, and a PPAR agonist in the manufacture of a medicament for treating or ameliorating a pediatric cholestatic liver disease.

61. The use of claim 60, wherein the subclinical therapeutically effective amount of the second therapeutic agent is at least 10% lower than the amount of the second therapeutic agent to be administered as a monotherapy.
62. The use of claim 60, wherein the subclinical therapeutically effective amount of the second therapeutic agent is at least 20% than the amount of the second therapeutic agent to be administered a monotherapy.
63. The use of claim 60, wherein the second therapeutic agent is UDCA or rifampicin.
64. The use of claim 60, wherein the subject discontinues the administration of the second therapeutic agent without increasing pruritus.
65. The use of claim 60, wherein the second therapeutic agent is a PPAR agonist.
66. The use of claim 65, wherein the PPAR agonist is selected from bezafibrate, seladelpar (MBX-8025), GW501516 (Cardarine), fenofibrate, elafibranor, REN001, KD3010, ASP0367, and CER-002.
67. The use of claim 65, wherein the PPAR agonist is a PPARδ agonist.
68. The use of claim 67, wherein the PPARδ agonist is selected from seladelpar (MBX-8025), REN001, KD3010, ASP0367, and CER-002.
69. Use of maralixibat in combination with a PPAR agonist in the manufacture of a medicament for treating or ameliorating a pediatric cholestatic liver disease.
70. The use of claim 69, wherein the PPAR agonist is selected from bezafibrate, seladelpar (MBX-8025), GW501516 (Cardarine), fenofibrate, elafibranor, REN001, KD3010, ASP0367, and CER-002.
71. The use of claim 69, wherein the PPAR agonist is a PPARδ agonist.
72. The use of claim 71, wherein the PPARδ agonist is selected from seladelpar (MBX-8025), REN001, KD3010, ASP0367, and CER-002.
73. The use of claim 69, wherein the pediatric cholestatic liver disease is sclerosing cholangitis.
74. The use of claim 69, wherein the pediatric cholestatic liver disease is selected from PSC and PBC.