BILE ACID RECYCLING INHIBITORS FOR TREATMENT OF PEDIATRIC CHOLESTATIC LIVER DISEASES

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 61/553,094, filed October 28, 2011, U.S. Provisional Application No. 61/607,487, filed March 6, 2012, U.S. Provisional Application No. 61/607,503, filed March 6, 2012, which are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

[0002] 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. An effective and less invasive treatment that is suitable for the pediatric population is not available.

[0003] 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 cholestastatic liver diseases are needed.

SUMMARY

[0004] The present invention refers to subject matter as defined in the attached set of claims. Described herein are therapeutic compositions and methods for treating or ameliorating a pediatric cholestatic liver disease or pediatric cholestasis. In certain examples, described herein are methods for treating or ameliorating a pediatric cholestatic liver disease comprising non-systemically administering to a pediatric patient a therapeutically effective amount of a composition comprising an Apical Sodium-dependent Bile Transporter Inhibitor (ASBTI) or a pharmaceutically acceptable salt thereof. In certain examples, described herein are methods for treating or ameliorating a pediatric cholestatic liver disease comprising administering to an individual in need thereof a therapeutically effective amount of a composition comprising a non-systemically absorbed ASBTI or a pharmaceutically acceptable salt thereof. In certain examples, described herein are methods for treating or ameliorating a pediatric cholestatic liver disease comprising non-systemically administering to a pediatric patient a therapeutically effective amount of a pediatric dosage form comprising an Apical Sodium-dependent Bile Transporter Inhibitor (ASBTI) or a pharmaceutically acceptable salt thereof. In certain examples, described herein are methods for treating or ameliorating a pediatric cholestatic liver disease comprising administering to an individual in need thereof a therapeutically effective amount of a pediatric dosage form comprising a non-systemically absorbed ASBTI or a pharmaceutically acceptable salt thereof.

[0005] In certain examples, described herein are pediatric dosage forms comprising a pediatric dosage of a non-systemically absorbed Apical Sodium-dependent Bile Acid Transporter Inhibitor (ASBTI) or a pharmaceutically acceptable salt thereof. In some examples, described herein are pediatric dosage forms comprising any non-systemically absorbed ASBTI or a pharmaceutically acceptable salt thereof described herein. In some examples, described herein are pediatric dosage forms comprising any non-systemically absorbed ASBTI or a pharmaceutically acceptable salt thereof and a second agent described herein.

[0006] Described herein are therapeutic compositions and methods for treating or ameliorating pruritis. In certain examples, described herein are methods for treating or ameliorating pruritis comprising non-systemically administering to a pediatric patient suffering from a pediatric cholestatic liver disease a therapeutically effective amount of a composition comprising an ASBTI or a pharmaceutically acceptable salt thereof. In certain examples, described herein are methods for treating or ameliorating pruritis comprising administering to an individual in need thereof a therapeutically effective amount of a composition comprising a non-systemically absorbed ASBTI or a pharmaceutically acceptable salt thereof. In certain examples, described herein are methods for treating or ameliorating pruritis comprising non-systemically administering to a pediatric patient suffering from a pediatric cholestatic liver disease a therapeutically effective amount of a pediatric dosage form comprising an ASBTI or a pharmaceutically acceptable salt thereof. In certain examples, described herein are methods for treating or ameliorating pruritis comprising administering to an individual in need thereof a therapeutically effective amount of a pediatric dosage form comprising a non-systemically absorbed ASBTI or a pharmaceutically acceptable salt thereof.

[0007] Described herein are therapeutic compositions and methods for treating or ameliorating pediatric hypercholemia. In certain examples, described herein are methods for treating or ameliorating pediatric hypercholemia comprising non-systemically administering to a pediatric patient a therapeutically effective amount of a composition comprising an ASBTI or a pharmaceutically acceptable salt thereof. In certain examples, described herein are methods for treating or ameliorating pediatric hypercholemia comprising administering to an individual in need thereof a therapeutically effective amount of a composition comprising a non-systemically absorbed ASBTI or a pharmaceutically acceptable salt thereof. In certain examples, described herein are methods for treating or ameliorating pediatric hypercholemia comprising non-systemically administering to a pediatric patient a therapeutically effective amount of a pediatric dosage form comprising an ASBTI or a pharmaceutically acceptable salt thereof. In certain examples, described herein are methods for treating or ameliorating pediatric hypercholemia comprising administering to an individual in need thereof a therapeutically effective amount of a pediatric dosage form comprising a non-systemically absorbed ASBTI or a pharmaceutically acceptable salt thereof.

[0008] Described herein are therapeutic compositions and methods for lowering serum bile acid concentrations or hepatic bile acid concentrations. In certain examples, described herein are methods for decreasing serum bile acid levels or concentrations or hepatic bile acid levels or concentrations comprising non-systemically administering to a pediatric patient suffering from a pediatric cholestatic liver disease a

therapeutically effective amount of a composition comprising an ASBTI or a pharmaceutically acceptable salt thereof. In certain examples, described herein are methods for decreasing serum bile acids or hepatic bile acids comprising administering to an individual in need thereof a therapeutically effective amount of a composition comprising a non-systemically absorbed ASBTI or a pharmaceutically acceptable salt thereof. In certain examples, described herein are methods for decreasing serum bile acid levels or concentrations or hepatic bile acid levels or concentrations comprising non-systemically administering to a pediatric patient suffering from a pediatric cholestatic liver disease a therapeutically effective amount of a pediatric dosage form comprising an ASBTI or a pharmaceutically acceptable salt thereof. In certain examples, described herein are methods for decreasing serum bile acids or hepatic bile acids comprising administering to an individual in need thereof a therapeutically effective amount of a pediatric dosage form comprising a non-systemically absorbed ASBTI or a pharmaceutically acceptable salt thereof.

[0009] In some examples, compositions and methods described herein decrease serum or hepatic bile acid levels by at least 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, or 10%, as compared to the levels prior to administration of the compositions described herein or as compared to control subjects. In some examples, methods described herein decrease serum or hepatic bile acid levels by at least 30%. In some examples, methods described herein decrease serum or hepatic bile acid levels by at least 25%. In some examples, methods described herein decrease serum or hepatic bile acid levels by at least 20%. In some examples, methods described herein decrease serum or hepatic bile acid levels by at least 15%.

[0010] Described herein are therapeutic compositions and methods for treating or ameliorating xanthoma. In certain examples, described herein are methods for treating or ameliorating xanthoma comprising non-systemically administering to a pediatric patient suffering from a pediatric cholestatic liver disease a therapeutically effective amount of a composition comprising an ASBTI or a pharmaceutically acceptable salt thereof. In certain examples, described herein are methods for treating or ameliorating xanthoma comprising administering to an individual in need thereof a therapeutically effective amount of a composition comprising a non-systemically absorbed ASBTI or a pharmaceutically acceptable salt thereof. In certain examples, described herein are methods for treating or ameliorating xanthoma comprising non-systemically administering to a pediatric patient suffering from a pediatric cholestatic liver disease a therapeutically effective amount of a pediatric dosage form comprising an ASBTI or a pharmaceutically acceptable salt thereof. In certain examples, described herein are methods for treating or ameliorating xanthoma comprising administering to an individual in need thereof a therapeutically effective amount of a pediatric dosage form comprising a non-systemically absorbed ASBTI or a pharmaceutically acceptable salt thereof.

[0011] In some examples, described herein are compositions and methods decreasing serum lipoprotein X levels or concentrations comprising non-systemically administering to a pediatric patient suffering from xanthoma a therapeutically effective amount of a composition comprising an ASBTI or a pharmaceutically acceptable salt thereof. In certain examples, described herein are methods for decreasing serum lipoprotein X comprising administering to an individual in need thereof a therapeutically effective amount of

a composition comprising a non-systemically absorbed ASBTI or a pharmaceutically acceptable salt thereof. In certain examples, described herein are methods for decreasing serum lipoprotein X levels or concentrations comprising non-systemically administering to a pediatric patient suffering from xanthoma a therapeutically effective amount of a pediatric dosage form comprising an ASBTI or a pharmaceutically acceptable salt thereof. In certain examples, described herein are methods for decreasing serum lipoprotein X comprising administering to an individual in need thereof a therapeutically effective amount of a pediatric dosage form comprising a non-systemically absorbed ASBTI or a pharmaceutically acceptable salt thereof.

[0012] In certain examples, described herein are compositions and methods for reducing serum levels of bilirubin, gamma-glutamyl transpeptidase or gamma-glutamyl transferase (GGT), or liver enzymes, such as alkaline phosphatase, ALT and AST, in an individual in need thereof comprising non-systemically administering a therapeutically effective amount of a composition of an ASBTI or a pharmaceutically acceptable salt thereof. In some examples, methods comprise administering a therapeutically effective amount of a composition comprising a non-systemically absorbed ASBTI or a pharmaceutically acceptable salt thereof. In certain examples, described herein are methods for reducing serum levels of bilirubin, gamma-glutamyl transpeptidase or gamma-glutamyl transferase (GGT), or liver enzymes, such as alkaline phosphatase, ALT and AST, in an individual in need thereof comprising non-systemically administering a therapeutically effective amount of a pediatric dosage form of an ASBTI or a pharmaceutically acceptable salt thereof. In some examples, methods comprise administering a therapeutically effective amount of a pediatric dosage form comprising a non-systemically absorbed ASBTI or a pharmaceutically acceptable salt thereof.

[0013] In certain examples, methods described herein comprise administering compounds that inhibit the ASBT or any recuperative bile salt transporter. In certain examples, use of the compounds described herein reduces or inhibits recycling of bile acid salts in the gastrointestinal tract. In some examples, the methods described herein reduce intraenterocyte bile acids/salts or reduce necrosis and/or damage to intestinal or hepatocellular architecture.

[0014] In certain examples, the methods described herein treat or ameliorate a pediatric cholestatic liver disease by increasing intraluminal concentrations of bile acids/salts, which are then excreted in the feces, thereby reducing overall bile acid and serum bile acid or hepatic bile acid load in an individual in need thereof. In certain examples, increasing intraluminal bile acid concentrations according to methods described herein provide protection and/or control of the integrity of an individual's liver and/or intestine that has been injured by cholestasis and/or cholestatic liver disease.

[0015] In certain examples, the methods described herein treat or ameliorate pruritis by increasing intraluminal concentrations,and/or reducing serum concentrations, or hepatic concentrations of bile acids/salts in an individual in need thereof. In certain examples, increasing intraluminal bile acid concentrations according to methods described herein provide protection and/or control of the integrity of an individual's liver and/or intestine that has been injured by a cholestatic liver disease.

[0016] In certain examples, the methods described herein lower serum bile acid concentrations or hepatic bile acid concentrations by increasing intraluminal concentrations of bile acids/salts in an individual in need thereof. In certain examples, increasing intraluminal bile acid concentrations according to methods described herein provide protection and/or control of the integrity of an individual's liver and/or intestine that has been injured by a cholestatic liver disease.

[0017] In certain examples, described herein is an ASBTI or a pharmaceutically acceptable salt thereof for use in the treatment of a pediatric cholestatic liver disease, wherein the ASBTI is non-systemically absorbed or is formulated to be non-systemically absorbed. In some examples, described herein is a pharmaceutical composition for use in the treatment of a pediatric cholestatic liver disease, wherein the composition comprises a pediatric dosage form of an ASBTI and a pharmaceutically acceptable excipient, wherein the ASBTI is non-systemically absorbed or is formulated to be non-systemically absorbed. In some examples, a composition described herein is suitable for non-systemically administering to the distal ileum, colon, and/or rectum.

[0018] In certain examples, described herein is an ASBTI or a pharmaceutically acceptable salt thereof for use in the treatment of pruritis in a pediatric patient suffering from a pediatric cholestatic liver disease, wherein the ASBTI is non-systemically absorbed or is formulated to be non-systemically absorbed. In some examples, described herein is a pharmaceutical composition for use in the treatment of pruritis, wherein the composition comprises a pediatric dosage form of an ASBTI and a pharmaceutically acceptable excipient, wherein the ASBTI is non-systemically absorbed or is formulated to be non-systemically absorbed. In some examples, a composition described herein is suitable for non-systemically administering to the distal ileum, colon, and/or rectum.

[0019] In certain examples, described herein is an ASBTI or a pharmaceutically acceptable salt thereof for use in lowering serum bile acid concentrations or hepatic bile acid concentrations in a pediatric patient suffering from a pediatric cholestatic liver disease, wherein the ASBTI is a non-systemically absorbed or is formulated to be non-systemically absorbed. In some examples, described herein is a pharmaceutical composition for use in lowering serum bile acid concentrations or hepatic bile acid concentrations, wherein the composition comprises a pediatric dosage form of an ASBTI and a pharmaceutically acceptable excipient, wherein the ASBTI is non-systemically absorbed or is formulated to be non-systemically absorbed. In some examples, a composition described herein is suitable for non-systemically administering to the distal ileum, colon, and/or rectum.

[0020] In some examples, an ASBTI described herein is minimally absorbed or formulated to be minimally absorbed. In some examples, a pediatric dosage form of an ASBTI is non-systemically administered to the distal ileum, colon, and/or rectum of an individual in need thereof. In some examples, an ASBTI is non-systemically administered to the ileum, colon or rectum of an individual in need thereof. In some examples, less than 50%, less than 40%, less than 30%, less than 20%, less than 10%, less than 9%, less than 8%, less than 7%, less than 6%, less than 5%, less than 4%, less than 3%, less than 2%, or less than 1% of the ASBTI is systemically absorbed. In a preferred embodiment, less than 10%

of the ASBTI is systemically absorbed. In another preferred embodiment, less than 5% of the ASBTI is systemically absorbed. In another preferred embodiment, less than 1% of the ASBTI is systemically absorbed.

[0021] In one example, described herein is a method for treating a pediatric cholestatic liver disease in an individual in need thereof comprising non-systemically administering to the distal gastrointestinal tract of the individual in need thereof a therapeutically effective amount of a pediatric dosage form of an ASBTI or a pharmaceutically acceptable salt thereof. In one example, described herein is a method for treating pruritis in an individual in need thereof comprising non-systemically administering to the distal gastrointestinal tract of the individual in need thereof a therapeutically effective amount of a pediatric dosage form of an ASBTI or a pharmaceutically acceptable salt thereof. In one example, described herein is a method for lowering serum bile acid concentrations in an individual in need thereof comprising non-systemically administering to the distal gastrointestinal tract of the individual in need thereof a therapeutically effective amount of a pediatric dosage form of an ASBTI or a pharmaceutically acceptable salt thereof. In some examples, the distal gastrointestinal tract is jejunum, ileum, colon, or rectum. In some examples, the distal gastrointestinal tract is ileum, colon, or the rectum. In some examples, the distal gastrointestinal tract is jejunum. In some examples, the distal gastrointestinal tract is ileum.

[0022] In certain examples, the pediatric cholestatic liver disease is progressive familial intrahepatic cholestasis (PFIC), PFIC type 1, PFIC type 2, PFIC type 3, Alagille syndrome, Dubin-Johnson Syndrome, biliary atresia, post-Kasai biliary atresia, post-liver transplantation biliary atresia, post-liver transplantation cholestasis, post-liver transplantation associated liver disease, intestinal failure associated liver disease, bile acid mediated liver injury, pediatric primary sclerosing cholangitis, 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), BRIP 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. In some examples, the pediatric cholestatic liver disease is a pediatric form of liver disease described herein.

[0023] In certain examples, a pediatric cholestatic liver disease is characterized by one or more symptoms selected from jaundice, pruritis, 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/or renal failure.

[0024] In certain examples, the pediatric patient is a new born, a pre-term new born, an infant, a toddler, a pre-schooler, a school-age child, a pre-pubescent child, post-pubescent child, an adolescent, or a teenager under the age of eighteen. In some examples, the pediatric patient is a new born, a pre-term new born, an infant, a toddler, a pre-schooler, or a school-age child. In some examples, the pediatric patient is a new born, a pre-term new born, an infant, a toddler, or a pre-schooler. In some examples, the pediatric patient is a new born, a pre-term new born, an infant, or a toddler. In some examples, the pediatric patient is a new born, a pre-term new born, or an infant. In some examples, the pediatric patient is a new born. In some examples, the pediatric patient is an infant. In some examples, the pediatric patient is a toddler.

[0025] In certain examples, the individual is an infant less than 2 years of age. In some cases, for any of the methods and/or compositions described herein, the individual is an infant between 0 to 18 months of age. In some cases, for any of the methods and/or compositions described herein, the individual is an infant between 1 to 18 months of age. In some cases, for any of the methods and/or compositions described herein, the individual is an infant between 2 to 18 months of age. In some cases, for any of the methods and/or compositions described herein, the individual is an infant between 3 to 18 months of age. In some cases, for any of the methods and/or compositions described herein, the individual is an infant between 4 to 18 months of age. In some cases, for any of the methods and/or compositions described herein, the individual is an infant between 6 to 18 months of age. In some cases, for any of the methods and/or compositions described herein, the individual is an infant between 18 to 24 months of age. In some cases, for any of the methods and/or compositions described herein, the individual is an infant between 6 to 12 months of age. In some instances, for any of the methods and/or compositions described herein, the individual is a child of between about 2 to about 10 years of age. In some instances, the individual is less than about 10 years old. In some instances, the individual is between about 10 to about 17 years old.

[0026] In some cases, for any of the methods and/or compositions described herein, the individual is a child between 6 months to 12 years of age.

[0027] Described herein, in certain examples, are therapeutic methods and compositions using compounds that inhibit the Apical Sodium-dependent Bile Transporter (ASBT) or a pharmaceutically acceptable salt thereof, or any recuperative bile salt transporter for treatment of a pediatric cholestatic liver disease or pruritis or for lowering serum bile acid concentrations. In certain instances, use of the compounds described herein reduces or inhibits recycling of bile acid salts in the gastrointestinal tract. In some examples, the methods described herein reduce intraenterocyte bile acids/salts and/or damage to ileal or hepatocellular architecture caused by a pediatric cholestatic liver disease and/or allow for regeneration of the intestinal lining or liver. In some examples, the bile transport inhibitors are non-systemic compounds. In other examples, the bile acid transporter inhibitors are systemic compounds delivered non-systemically. In other examples, the bile acid transporter inhibitors are systemic compounds. In certain examples, the bile transport inhibitors described herein enhance enteroendocrine peptide secretion by intestinal L-cells.

[0028] In some examples of the methods described above, the ASBTI is a compound of Formula I or a pharmaceutically acceptable salt thereof, as described herein. In some examples of the methods described above, the ASBTI is a compound of Formula II or a pharmaceutically acceptable salt thereof, as described herein. In some examples of the methods described above, the ASBTI is a compound of Formula III or a pharmaceutically acceptable salt thereof, as described herein. In some examples of the methods described above, the ASBTI is a compound of Formula IV or a pharmaceutically acceptable salt thereof, as described herein. In some examples of the methods described above, the ASBTI is a compound of Formula V or a pharmaceutically acceptable salt thereof, as described herein. In some examples of the methods described above, the ASBTI is a compound of Formula VI or Formula VID or a pharmaceutically acceptable salt thereof, as described herein.

[0029] In some examples, described herein is a method for treating or ameliorating a pediatric cholestatic liver disease comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of a pediatric dosage form of an ASBTI of Formula I or a pharmaceutically acceptable salt thereof. In some examples, described herein is a method for treating or ameliorating pruritis comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of a pediatric dosage form of an ASBTI of Formula I or a pharmaceutically acceptable salt thereof. In some examples, described herein is a method for increasing the levels of an enteroendocrine peptide or hormone in an individual suffering from a pediatric cholestatic liver disease comprising non-systemically administering to the individual in need thereof a therapeutically effective amount of a pediatric dosage form of an ASBTI of Formula I or a pharmaceutically acceptable salt thereof. In some examples, described herein is a method for lowering serum bile acid concentrations or hepatic bile acid concentration comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of a pediatric dosage form of an ASBTI of Formula I or a pharmaceutically acceptable salt thereof.

[0030] In some examples, described herein is a method for treating or ameliorating a pediatric cholestatic liver disease comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of a pediatric dosage form of an ASBTI of Formula II or a pharmaceutically acceptable salt thereof. In some examples, described herein is a method for treating or ameliorating pruritis comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of a pediatric dosage form of an ASBTI of Formula II or a pharmaceutically acceptable salt thereof. In some examples, described herein is a method for increasing the levels of an enteroendocrine peptide or hormone in an individual suffering from a pediatric cholestatic liver disease comprising non-systemically administering to the individual in need thereof a therapeutically effective amount of a pediatric dosage form of an ASBTI of Formula II or a pharmaceutically acceptable salt thereof. In some examples, described herein is a method for lowering serum bile acid concentrations or hepatic bile acid concentration comprising non-systemically administering to an individual in need thereof a therapeutically

effective amount of a pediatric dosage form of an ASBTI of Formula II or a pharmaceutically acceptable salt thereof.

[0031] In some examples, described herein is a method for treating or ameliorating a pediatric cholestatic liver disease comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of a pediatric dosage form of an ASBTI of Formula III or a pharmaceutically acceptable salt thereof. In some examples, described herein is a method for treating or ameliorating pruritis comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of a pediatric dosage form of an ASBTI of Formula III or a pharmaceutically acceptable salt thereof. In some examples, described herein is a method for increasing the levels of an enteroendocrine peptide or hormone in an individual suffering from a pediatric cholestatic liver disease comprising non-systemically administering to the individual in need thereof a therapeutically effective amount of a pediatric dosage form of an ASBTI of Formula III or a pharmaceutically acceptable salt thereof. In some examples, described herein is a method for lowering serum bile acid concentrations or hepatic bile acid concentration comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of a pediatric dosage form of an ASBTI of Formula III or a pharmaceutically acceptable salt thereof.

[0032] In some examples, described herein is a method for treating or ameliorating a pediatric cholestatic liver disease comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of a pediatric dosage form of an ASBTI of Formula IV or a pharmaceutically acceptable salt thereof. In some examples, described herein is a method for treating or ameliorating pruritis comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of a pediatric dosage form of an ASBTI of Formula IV or a pharmaceutically acceptable salt thereof. In some examples, described herein is a method for increasing the levels of an enteroendocrine peptide or hormone in an individual suffering from a pediatric cholestatic liver disease comprising non-systemically administering to the individual in need thereof a therapeutically effective amount of a pediatric dosage form of an ASBTI of Formula IV or a pharmaceutically acceptable salt thereof. In some examples, described herein is a method for lowering serum bile acid concentrations or hepatic bile acid concentration comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of a pediatric dosage form of an ASBTI of Formula IV or a pharmaceutically acceptable salt thereof.

[0033] In some examples, described herein is a method for treating or ameliorating a pediatric cholestatic liver disease comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of a pediatric dosage form of an ASBTI of Formula V or a pharmaceutically acceptable salt thereof. In some examples, described herein is a method for treating or ameliorating pruritis comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of a pediatric dosage form of an ASBTI of Formula V or a pharmaceutically acceptable salt thereof. In some examples, described herein is a method for increasing

the levels of an enteroendocrine peptide or hormone in an individual suffering from a pediatric cholestatic liver disease comprising non-systemically administering to the individual in need thereof a therapeutically effective amount of a pediatric dosage form of an ASBTI of Formula V or a pharmaceutically acceptable salt thereof. In some examples, described herein is a method for lowering serum bile acid concentrations or hepatic bile acid concentration comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of a pediatric dosage form of an ASBTI of Formula V or a pharmaceutically acceptable salt thereof.

[0034] In some examples, described herein is a method for treating or ameliorating a pediatric cholestatic liver disease comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of a pediatric dosage form of an ASBTI of Formula VI or a pharmaceutically acceptable salt thereof. In some examples, described herein is a method for treating or ameliorating pruritis comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of a pediatric dosage form of an ASBTI of Formula VI or a pharmaceutically acceptable salt thereof. In some examples, described herein is a method for increasing the levels of an enteroendocrine peptide or hormone in an individual suffering from a pediatric cholestatic liver disease comprising non-systemically administering to the individual in need thereof a therapeutically effective amount of a pediatric dosage form of an ASBTI of Formula VI or a pharmaceutically acceptable salt thereof. In some examples, described herein is a method for lowering serum bile acid concentrations or hepatic bile acid concentration comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of a pediatric dosage form of an ASBTI of Formula VI or a pharmaceutically acceptable salt thereof.

[0035] In certain examples, an ASBTI is any compound described herein that inhibits recycling of bile acids/salts in the gastrointestinal tract of an individual. In certain examples, an ASBTI is (-)-(3R, 5R)-trans-3-butyl-3-ethyl-2,3,4,5-tetrahydro-7,8-dimethoxy-5-phenyl-1,4-benzothiazepine1,1-dioxide; ("Compound 100A") or any other salt or analog thereof. In certain of any of the aforementioned examples, an ASBTI is 1-[4-[4-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]butyl]4-aza-1-azoniabicyclo[2.2.2]octane methane sulfonate salt ("Compound 100B") or any other salt or analog thereof. In certain examples, an ASBTI is *N*, *N*-dimethylimido-dicarbonimidic diamide ("Compound 100C") or any salt or analog thereof. In certain examples, an ASBTI is any commercially available ASBTI including but not limited to SD-5613, A-3309, 264W94, S-8921, SAR-548304, BARI-1741, HMR-1453, TA-7552, R-146224, or SC-435. In some examples, an ASBTI is 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N-((R)-1-carboxy-2-methylthio-ethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)- α-[N-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)- α- [N-((S)-1-carboxy-2-methylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5- tetrahydro-1,2,5-

benzothiadiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α- [N-((S)-1-carboxybutyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N-((S)-1-carboxypropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)- α-[N-((S)-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N-((S)-1-carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N-((R)-1-carboxy-2-methylthioethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N-{(S)-1-[N-((S)-2-hydroxy-1-carboxyethyl)carbamoyl]propyl}carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N-((S)-1-carboxy-2-methylpropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N-((S)-1-carboxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-{(R)-α-carboxy4-hydroxybenzyl}carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; or 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N-(carboxymethyl)carbamoyl]benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{ (R)-1'-phenyl-1'-[N'-(carboxymethyl) carbamoyl] methyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxypropyl)carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{ (R)-1'-phenyl-1'-[N'-(carboxymethyl) carbamoyl] methyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxyethyl)carbamoyl]benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; or a pharmaceutically acceptable salt thereof; 1-[[5-[[3-[(3S,4R,5R)-3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5yl]phenyl]amino]-5-oxopentyl]amino]-1-deoxy-D-glucitol; or Potassium((2R,3R,4S,5R,6R)-4-benzyloxy-6-{3-[3-((3S,4R,5R)-3-butyl-7-dimethylamino-3-ethyl-4-hydroxy-1,1-dioxo-2,3,4,5-tetrahydro-1H-benzo[b]thiepin-5-yl)-phenyl]-ureido}-3,5-dihydroxy-tetrahydro-pyran-2-ylmethyl)sulphate ethanolate, hydrate. In certain examples, an ASBTI is 264W94 (Glaxo), SC-435 (Pfizer), SD-5613 (Pfizer), or A3309 (Astra-Zeneca).

[0036] In certain examples, methods described herein further comprise administration of a second agent selected from ursodiol, UDCA, cholestyramine/resins, antihistamine agents (e.g., hydroxyzine, diphenhydamine), rifampin, nalaxone, Phenobarbital, dronabinol (CB1 agonist), methotrexate, corticosteroids, cyclosporine, colchicines, TPGS - vitamin A, D, E, or K optionally with polyethylene glycol, zinc, and a resin or sequestrant for absorbing bile acids or an analog thereof. In certain examples, methods described herein further comprise administration of a second agent selected from a bile acid or salt with reduced toxicity or a hydrophilic bile acid such as ursodiol, norursodiol, ursodeoxycholic acid, chenodeoxycholic acid, cholic acid, taurocholic acid, ursocholic acid, glycocholic acid, glycodeoxycholic acid, taurodeoxycholic acid, taurocholate, glycochenodeoxycholic acid, or tauroursodeoxycholic acid.

[0037] In certain examples, described herein are pediatric dosage forms such as a solution, syrup, suspension, elixir, powder for reconstitution as suspension or solution, dispersible/effervescent tablet, chewable tablet, gummy candy, lollipop, freezer pops, troches, oral thin strips, orally disintegrating tablet, sachet, soft gelatin capsule, and sprinkle oral powder or granules.

[0038] In some examples, the pediatric dosage of an ASBTI is between about 1 µg/kg/day and about 10 mg/kg/day. In some examples, the pediatric dosage of an ASBTI is between about 5 µg/kg/day and about 1 mg/kg/day. In some examples, the pediatric dosage of an ASBTI is between about 10 µg/kg/day and about 300 µg/kg/day. In some examples, the pediatric dosage of an ASBTI is any dosage from about 14 µg/kg/day and about 280 µg/kg/day. In some examples, the pediatric dosage of an ASBTI is any dosage from about 14 µg/kg/day and about 140 µg/kg/day. In some examples, the pediatric dosage of an ASBTI is between about 5 µg/kg/day and about 200 µg/kg/day. In some examples, the pediatric dosage of an ASBTI is between about 10 µg/kg/day and about 200 µg/kg/day. In some examples, the pediatric dosage of an ASBTI is between about 10 µg/kg/day and about 175 µg/kg/day. In some examples, the pediatric dosage of an ASBTI is between about 10 µg/kg/day and about 150 µg/kg/day. In some examples, the pediatric dosage of an ASBTI is between about 10 µg/kg/day and about 140 µg/kg/day. In some examples, the pediatric dosage of an ASBTI is between about 25 µg/kg/day and about 140 µg/kg/day. In some examples, the pediatric dosage of an ASBTI is between about 50 µg/kg/day and about 140 µg/kg/day. In some examples, the pediatric dosage of an ASBTI is between about 70 µg/kg/day and about 140 µg/kg/day. In some examples, the pediatric dosage of an ASBTI is between about 10 µg/kg/day and about 100 µg/kg/day. In some examples, the pediatric dosage of an ASBTI is 10 µg/kg/day. In some examples, the pediatric dosage of an ASBTI is 20 µg/kg/day. In some examples, the pediatric dosage of an ASBTI is 30 µg/kg/day. In some examples, the pediatric dosage of an ASBTI is 35 µg/kg/day. In some examples, the pediatric dosage of an ASBTI is 40 µg/kg/day. In some examples, the pediatric dosage of an ASBTI is 50 µg/kg/day. In some examples, the pediatric dosage of an ASBTI is 60 µg/kg/day. In some examples, the pediatric dosage of an ASBTI is 70 µg/kg/day. In some examples, the pediatric dosage of an ASBTI is 80 µg/kg/day. In some examples, the pediatric dosage of an ASBTI is 90 µg/kg/day. In some examples, the pediatric dosage of an ASBTI is 100 µg/kg/day. In some examples, the pediatric dosage of an ASBTI is 110 µg/kg/day. In some

examples, the pediatric dosage of an ASBTI is 120 µg/kg/day. In some examples, the pediatric dosage of an ASBTI is 130 µg/kg/day. In some examples, the pediatric dosage of an ASBTI is 140 µg/kg/day. In some examples, the pediatric dosage of an ASBTI is 150 µg/kg/day. In some examples, the pediatric dosage of an ASBTI is 175 µg/kg/day.

[0039] In some examples, described herein are pediatric dosages of anASBTI between 14 µg/kg/day and 140 µg/kg/day, or between 14 µg/kg/day and 280 µg/kg/day.

[0040] In some examples, the pediatric dosage of an ASBTI is between about 0.5 mg/day and about 40 mg/day. In some examples, the pediatric dosage of an ASBTI is between about 0.5 mg/day and about 30 mg/day. In some examples, the pediatric dosage of an ASBTI is between about 1 mg/day and about 20 mg/day. In some examples, the pediatric dosage of an ASBTI is between about 1 mg/day and about 10 mg/day. In some examples, the pediatric dosage of an ASBTI is between about 1 mg/day and about 5 mg/day. In some examples, the pediatric dosage of an ASBTI is 1 mg/day. In some examples, the pediatric dosage of an ASBTI is 5 mg/day. In some examples, the pediatric dosage of an ASBTI is 10 mg/day. In some examples, the pediatric dosage of an ASBTI is 20 mg/day. In some examples, the pediatric dosage of an ASBTI is between 0.5 mg/day and 5 mg/day. In some examples, the pediatric dosage of an ASBTI is between 0.5 mg/day and 4.5 mg/day. In some examples, the pediatric dosage of an ASBTI is between 0.5 mg/day and 4 mg/day. In some examples, the pediatric dosage of an ASBTI is between 0.5 mg/day and 3.5 mg/day. In some examples, the pediatric dosage of an ASBTI is between 0.5 mg/day and 3 mg/day. In some examples, the pediatric dosage of an ASBTI is between 0.5 mg/day and 2.5 mg/day. In some examples, the pediatric dosage of an ASBTI is between 0.5 mg/day and 2 mg/day. In some examples, the pediatric dosage of an ASBTI is between 0.5 mg/day and 1.5 mg/day. In some examples, the pediatric dosage of an ASBTI is between 0.5 mg/day and 1 mg/day. In some examples, the pediatric dosage of an ASBTI is between 1 mg/day and 4.5 mg/day. In some examples, the pediatric dosage of an ASBTI is between 1 mg/day and 4 mg/day. In some examples, the pediatric dosage of an ASBTI is between 1 mg/day and 3.5 mg/day. In some examples, the pediatric dosage of an ASBTI is between 1 mg/day and 3 mg/day. In some examples, the pediatric dosage of an ASBTI is between 1 mg/day and 2.5 mg/day. In some examples, the pediatric dosage of an ASBTI is between 1 mg/day and 2 mg/day. In some examples, the pediatric dosage of an ASBTI is 0.5 mg/day. In some examples, the pediatric dosage of an ASBTI is 1 mg/day. In some examples, the pediatric dosage of an ASBTI is 1.5 mg/day. In some examples, the pediatric dosage of an ASBTI is 2 mg/day. In some examples, the pediatric dosage of an ASBTI is 2.5 mg/day. In some examples, the pediatric dosage of an ASBTI is 3 mg/day. In some examples, the pediatric dosage of an ASBTI is 3.5 mg/day. In some examples, the pediatric dosage of an ASBTI is 4 mg/day. In some examples, the pediatric dosage of an ASBTI is 4.5 mg/day. In some examples, the pediatric dosage of an ASBTI is 5 mg/day. In some examples, the pediatric dosage described herein is the dosage of the total composition administered.

[0041] In some examples, the pediatric dosage form comprises 0.5 mg of the ASBTI. In some examples, the pediatric dosage form comprises 1 mg of the ASBTI. In some examples, the pediatric dosage form comprises 2.5 mg of the ASBTI. In some examples, the pediatric dosage form comprises 5 mg of the ASBTI. In some examples, the pediatric dosage form comprises 10 mg of the ASBTI. In some examples, the pediatric dosage form comprises 20 mg of the ASBTI.

[0042] In certain examples, the pediatric dosage of an ASBTI is given once a day. In some examples, the pediatric dosage of an ASBTI is given q.d. In some examples, the pediatric dosage of an ASBTI is given once a day in the morning. In some examples, the pediatric dosage of an ASBTI is given once a day at noon. In some examples, the pediatric dosage of an ASBTI is given once a day in the evening or night. In some examples, the pediatric dosage of an ASBTI is given twice a day. In some examples, the pediatric dosage of an ASBTI is given b.i.d. In some examples, the pediatric dosage of an ASBTI is given twice a day, in the morning and noon. In some examples, the pediatric dosage of an ASBTI is given twice a day, in the morning and evening. In some examples, the pediatric dosage of an ASBTI is given twice a day, in the morning and night. In some examples, the pediatric dosage of an ASBTI is given twice a day, at noon and in the evening. In some examples, the pediatric dosage of an ASBTI is given twice a day, at noon and in the night. In some examples, the pediatric dosage of an ASBTI is given three times a day. In some examples, the pediatric dosage of an ASBTI is given t.i.d. In some examples, the pediatric dosage of an ASBTI is given four times a day. In some examples, the pediatric dosage of an ASBTI is given q.i.d. In some examples, the pediatric dosage of an ASBTI is given every four hours. In some examples, the pediatric dosage of an ASBTI is given q.q.h. In some examples, the pediatric dosage of an ASBTI is given every other day. In some examples, the pediatric dosage of an ASBTI is given q.o.d. In some examples, the pediatric dosage of an ASBTI is given three times a week. In some examples, the pediatric dosage of an ASBTI is given t.i.w.

[0043] Described in certain examples herein are methods and dosage forms (e.g., oral or rectal dosage form) for use in the treatment of a pediatric cholestatic liver disease or pruritis, or lowering serum bile acid concentrations comprising a therapeutically effective amount of an ASBTI, or a pharmaceutically acceptable salt thereof, and a carrier. In some examples, described herein is a method for treating cholestasis and/or a cholestatic liver disease comprising orally administering a therapeutically effective amount of a minimally absorbed ASBTI , or a pharmaceutically acceptable salt thereof, to an individual in need thereof. In some examples, described herein is a method for treating cholestasis and/or a cholestatic liver disease comprising orally administering a therapeutically effective amount of a minimally absorbed ASBTI, or a pharmaceutically acceptable salt thereof, to an individual in need thereof. In some examples, the ASBTI, or salt thereof is a minimally absorbed ASBTI. In specific ~~embodiments~~examples, the dosage form is an enteric formulation, an ileal-pH sensitive release formulation, or a suppository or other suitable form.

[0044] In some ~~embodiments~~examples, a composition for use in the treatment of a pediatric cholestatic liver disease or pruritis, or lowering serum bile acid concentrations comprises at least one of a spreading agent or a wetting agent. In some ~~embodiments~~examples, the composition comprises an absorption inhibitor. In some cases an

absorption inhibitor is a mucoadhesive agent (e.g., a mucoadhesive polymer). In certain ~~embodiments~~examples, the mucoadhesive agent is selected from methyl cellulose, polycarbophil, polyvinylpyrrolidone, sodium carboxymethyl cellulose, and combinations thereof. In some ~~embodiments~~examples, the enteroendocrine peptide secretion enhancing agent is covalently linked to the absorption inhibitor. In certain ~~embodiments~~examples, the pharmaceutical composition comprises an enteric coating. In some ~~embodiments~~examples, a composition for use in treatment of cholestasis, a cholestatic liver disease or pruritis described above comprises a carrier. In certain ~~embodiments~~examples, the carrier is a rectally suitable carrier. In certain ~~embodiments~~examples, any pharmaceutical composition described herein is formulated as a suppository, an enema solution, a rectal foam, or a rectal gel. In some ~~embodiments~~examples, any pharmaceutical composition described herein comprises an orally suitable carrier.

[0045] In some ~~embodiments~~examples, a pediatric dosage form comprising an ASBTI is administered orally. In some ~~embodiments~~examples, the ASBTI is administered as an ileal-pH sensitive release formulation that delivers the ASBTI to the distal ileum, colon and/or rectum of an individual. In some ~~embodiments~~examples, the ASBTI is administered as an enterically coated formulation. In some ~~embodiments~~examples, oral delivery of an ASBTI ~~provided~~described herein can include formulations, as are well known in the art, to provide prolonged or sustained delivery of the drug to the gastrointestinal tract by any number of mechanisms. These include, but are not limited to, pH sensitive release from the dosage form based on the changing pH of the small intestine, slow erosion of a tablet or capsule, retention in the stomach based on the physical properties of the formulation, bioadhesion of the dosage form to the mucosal lining of the intestinal tract, or enzymatic release of the active drug from the dosage form. The intended effect is to extend the time period over which the active drug molecule is delivered to the site of action (the ileum) by manipulation of the dosage form. Thus, enteric-coated and enteric-coated controlled release formulations are within the scope of the present invention. Suitable enteric coatings include cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methacrylic acid methyl ester.

[0046] In some ~~embodiments~~examples, the methods and compositions ~~provided~~described herein further comprise administration of a bile acid sequestrant or binder for reducing gastrointestinal side effects. In some ~~embodiments~~examples, methods comprise administering a labile bile acid sequestrant, wherein the labile bile acid sequestrant has a low affinity in the colon or rectum of the individual for at least one bile acid. In some ~~embodiments~~examples, a labile bile acid sequestrant ~~provided~~described herein releases a bile acid in the colon or the rectum of a human. In some ~~embodiments~~examples, a labile bile acid sequestrant ~~provided~~described herein does not sequester a bile acid for excretion or elimination in feces. In some ~~embodiments~~examples, a labile bile acid sequestrant ~~provided~~described herein is a non-systemic labile bile acid sequestrant. In some ~~embodiments~~examples, non-systemic labile bile acid sequestrant is less than 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45% absorbed systemically. In some ~~embodiments~~examples, the labile bile acid sequestrant is lignin or a modified lignin. In some ~~embodiments~~examples, the labile bile acid sequestrant is a polycationic polymer or copolymer. In certain ~~embodiments~~examples, the labile bile acid sequestrant is a polymer or copolymer comprising one or more N-alkenyl-

N-alkylamine residues; one or more N,N,N-trialkyl-N-(N'-alkenylamino)alkyl-azanium residues; one or more N,N,N-trialkyl-N-alkenyl-azanium residues; one or more alkenyl-amine residues; cholestyramine, cholestipol, or cholesevelamor a combination thereof.

[0047] In some ~~embodiments~~examples of the methods described above, a pediatric dosage form comprising an ASBTI is administered before ingestion of food. In some ~~embodiments~~examples of the methods described above, a pediatric dosage form comprising an ASBTI is administered with or after ingestion of food.

[0048] In some ~~embodiments~~examples, the methods ~~provided~~described herein further comprise administration of vitamin supplements to compensate for reduced digestion of vitamins, in particular fat-soluble vitamins, in an individual with a pediatric cholestatic liver disease, pruritis, or elevated serum bile acid levels or concentrations. In some ~~embodiments~~examples, the vitamin supplements comprise fat-soluble vitamins. In some ~~embodiments~~examples, the fat-soluble vitamins are vitamin A, D, E, or K.

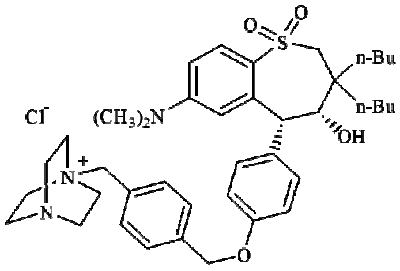
[0049] In some cases, for any of the methods described above, administration of an ASBTI reduces intraenterocyte bile acids/salts in an individual in need thereof. In some ~~embodiments~~examples, the methods described herein reduce accumulation of bile acids/salts in ileal enterocytes of an individual in need thereof. In some cases, for any of the methods described above, administration of an ASBTI inhibits transport of bile acids/salts from ileal lumen into enterocytes of an individual in need thereof. In some cases, for any of the methods described above, administration of an ASBTI increases ileal luminal bile acids/salts in an individual in need thereof. In some cases, for any of the methods described above, administration of an ASBTI reduces damage to intestinal (e.g., ileal cells) or hepatocellular (e.g., liver cells) architecture associated with a pediatric cholestatic liver disease or elevated serum or hepatic bile acid concentrations in an individual in need thereof. In some cases, for any of the methods described above, administration of an ASBTI regenerates intestinal lining or liver cells that have been injured by cholestasis and/or by a cholestatic liver disease in an individual suffering from a cholestatic liver disease.

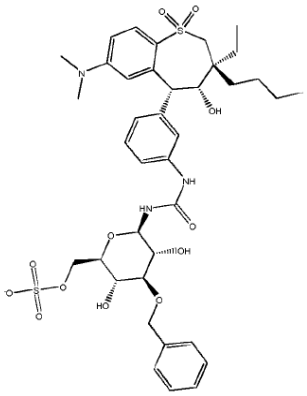
[0050] In some ~~embodiments~~examples, ~~provided~~described herein are methods for the treatment of a pediatric cholestatic liver disease comprising administration of a therapeutically effective amount of a pediatric dosage form comprising a combination of an ASBTI and ursodiol to an individual in need thereof. In some ~~embodiments~~examples, ~~provided~~described herein are methods for the treatment of a pediatric cholestatic liver disease comprising administration of a therapeutically effective amount of a combination of an ASBTI and a resin or sequestrant for absorbing bile acids to an individual in need thereof. In some ~~embodiments~~examples, an ASBTI is administered in combination with one or more agent selected from the group consisting of ursodiol, UDCA, ursodeoxycholic acid, chenodeoxycholic acid, cholic acid, taurocholic acid, ursocholic acid, glycocholic acid, glycodeoxycholic acid, taurodeoxycholic acid, taurocholate, glycochenodeoxycholic acid, tauroursodeoxycholic acid, cholestyramine/resins, antihistamine agents (e.g., hydroxyzine, diphenhydamine), rifampin, nalaxone, Phenobarbital, dronabinol (CB1 agonist), methotrexate, corticosteroids, cyclosporine, colchicines, TPGS - vitamin A, D, E, or K optionally with polyethylene glycol, zinc, a resin or sequestrant for absorbing bile acids.

[0051] In some examples, the methods described herein further comprise partial external biliary diversion (PEBD) therapy.

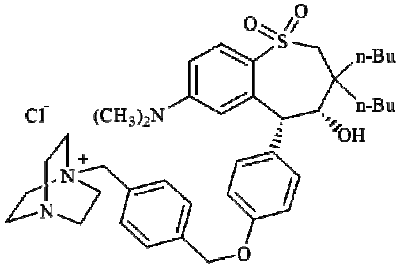
[0052] Described in some examples herein is a kit comprising any composition described herein (e.g., a pharmaceutical composition formulated for rectal administration) and a device for localized delivery within the rectum or colon. In certain examples, the device is a syringe, bag, or a pressurized container.

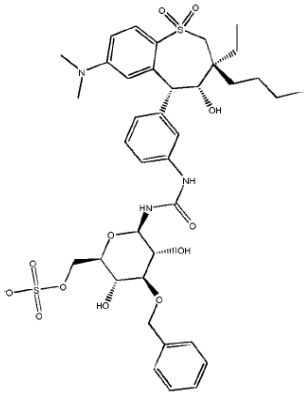
[0052a] In one aspect, the present disclosure refers to use of a composition comprising an Apical Sodium-dependent Bile Acid Transporter Inhibitor (ASBTI) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable diluent, excipient or carrier, in the manufacture of a medicament for treating a pediatric cholestatic liver disease in a pediatric patient between 0 and 18 years of age, wherein less than 10% of the ASBTI is systemically absorbed, and wherein the ASBTI is selected from



and .

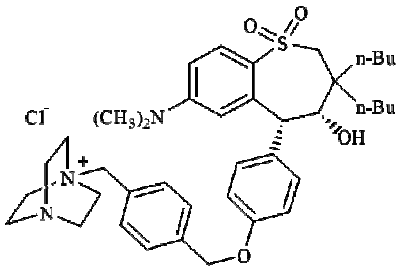
[0052b] In another aspect, the present disclosure refers to use of a composition comprising an Apical Sodium-dependent Bile Acid Transporter Inhibitor (ASBTI) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable diluent, excipient or carrier, in the manufacture of a medicament for treating pruritus in a pediatric patient between 0 and 18 years of age suffering from a pediatric cholestatic liver disease, wherein less than 10% of the ASBTI is systemically absorbed, and wherein the ASBTI is selected from

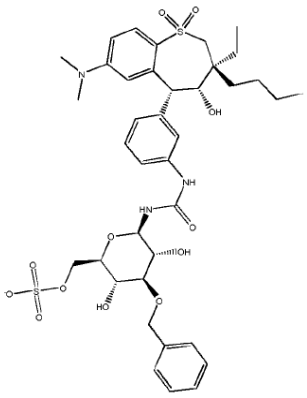


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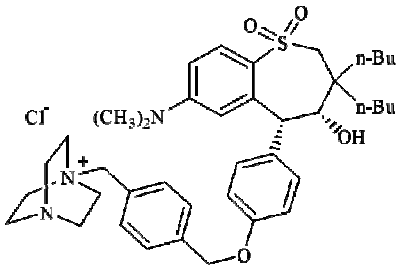
[0052c] In yet another aspect, the present disclosure refers to use of composition comprising an Apical Sodium-dependent Bile Acid Transporter Inhibitor (ASBTI) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable diluent, excipient or carrier, in the manufacture of a medicament for

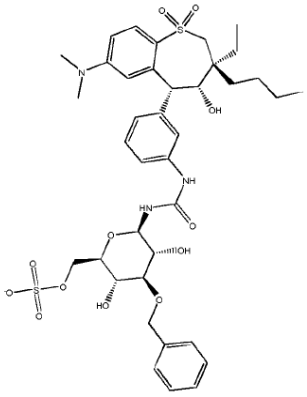
treating pediatric hypercholemia in a pediatric patient between 0 and 18 years of age, wherein less than 10% of the ASBTI is systemically absorbed, and wherein the ASBTI is selected from



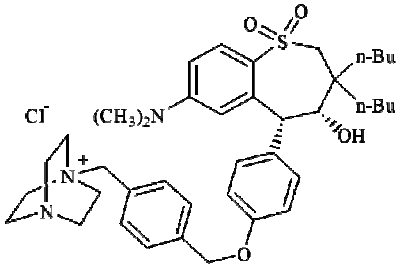
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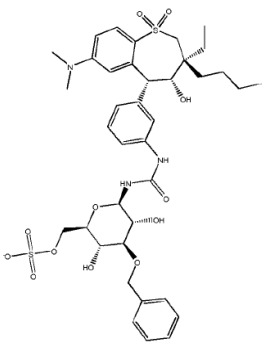
[0052d] In a further aspect, the present disclosure refers to use of a composition comprising an Apical Sodium-dependent Bile Acid Transporter Inhibitor (ASBTI) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable diluent, excipient or carrier, in the manufacture of a medicament for decreasing the level of serum bile acids or hepatic bile acids in a pediatric patient suffering from a pediatric cholestatic liver disease, wherein the pediatric patient is between 0 and 18 years of age, wherein less than 10% of the ASBTI is systemically absorbed, and wherein the ASBTI is selected from



and  .

[0052e] In another aspect, the present disclosure refers to a pediatric dosage form comprising a pediatric dosage of a non-systemically absorbed Apical Sodium-dependent Bile Acid Transporter Inhibitor (ASBTI) or a pharmaceutically acceptable salt thereof, wherein the ASBTI is a compound selected from



and  .

BRIEF DESCRIPTION OF THE DRAWINGS

[0053] FIGURE 1. Oral administration of 264W94 dose-dependently increased bile acids in the feces. Fecal bile acid concentrations were elevated up to 6.5 fold with an ED_{50} of 0.17 mg/kg, when compared to vehicle treated rats. Fecal NEFA also slightly increased in 264W94 treated rats. Plasma bile acid concentrations were decreased dose-dependently in 264W94 treated rats.

[0054] FIGURE 2. Plasma bile acid levels of ZDF rats after administration of ascending doses of SC-435 and LUM002. Male ZDF rats (n = 4) were administered vehicle, SC-435 (1, 10 or 30 mg/kg) or LUM002 (0.3, 1, 3, 10 or 30 mg/kg) by oral gavage twice a day for 2 weeks. Plasma bile acid levels were determined at the end of the second week. Data are expressed as mean values ± SEM.

[0055] FIGURE 3. Serum bile acid (SBA) analysis of healthy subjects after administration of ascending multiple oral doses of LUM001 a randomized, double-blind, placebo-controlled study. Shown in the graphs are data from the 0.5 (n=16), 1.0 (n=8), 2.5 (n=8), 5.0 (n=8) and 10 (n=8) mg dosing groups. On Day 1, blood was drawn for baseline SBA at approximately 30 minutes before and after breakfast and 30 minutes after lunch and dinner. Samples were obtained on day 14.

[0056] FIGURE 4. Fecal bile acid analysis of healthy subjects after administration of ascending multiple oral doses of LUM001 a randomized, double-blind, placebo-controlled study. Fecal samples were collected for all panels except the dose-titration panel, 2.5 (2) and 5 mg (2), on Days 9 through 14 and 23 through 28.

[0057] FIGURE 5. Fasting serum bile acid levels and morning post-prandial peak in children under the age of 12. LUM001 was administered once-a-day (QD) in the morning for fourteen days. The placebo patients had an average fasting serum bile acid level of 8.6 μmol/L and a post-prandial peak serum bile acid level of 11.9 μmol/L. For the LUM001 treated patients the values were 6.5 μmol/L and 9.2, respectively, representing a 24% and 23% decrease.

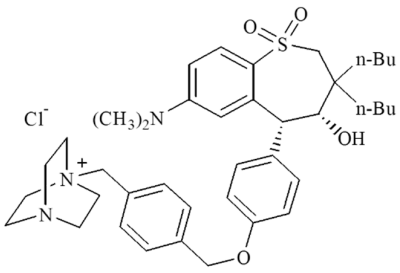
DETAILED DESCRIPTION OF THE INVENTION

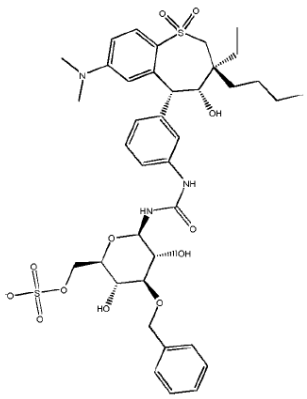
[0058] Bile acids/salts play a critical role in activating digestive enzymes and solubilizing fats and fat-soluble vitamins and are involved in liver, biliary, and intestinal disease. Bile acids are synthesized in the liver by a multistep, multiorganelle pathway. Hydroxyl groups are added to specific sites on the steroid structure, the double bond of the cholesterol B ring is reduced and the hydrocarbon chain is shortened by three carbon atoms resulting in a carboxyl group at the end of the chain. The most common bile acids are cholic acid and chenodeoxycholic acid (the “primary bile acids”). Before exiting the hepatocytes and forming bile, the bile acids are conjugated to either glycine (to produce glycocholic acid or glycochenodeoxycholic acid) or taurine (to produce taurocholic acid or taurochenodeoxycholic acid). The

CLAIMS

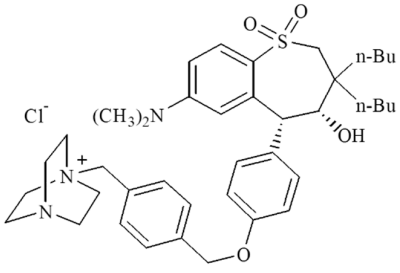
WHAT IS CLAIMED IS:

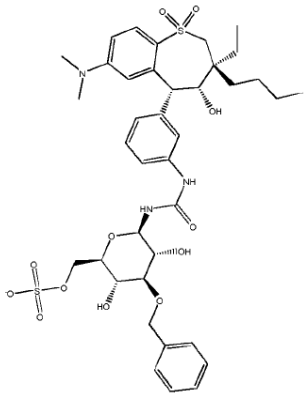
1. Use of a composition comprising an Apical Sodium-dependent Bile Acid Transporter Inhibitor (ASBTI) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable diluent, excipient or carrier, in the manufacture of a medicament for treating a pediatric cholestatic liver disease in a pediatric patient between 0 and 18 years of age, wherein less than 10% of the ASBTI is systemically absorbed, and wherein the ASBTI is selected from



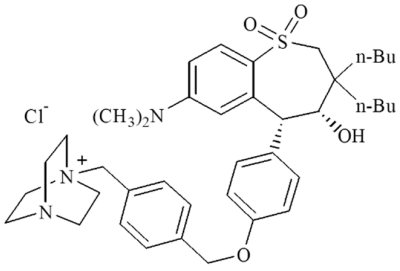
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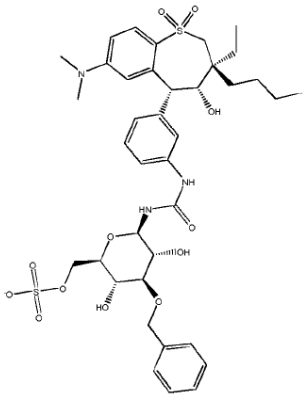
2. Use of a composition comprising an Apical Sodium-dependent Bile Acid Transporter Inhibitor (ASBTI) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable diluent, excipient or carrier, in the manufacture of a medicament for treating pruritus in a pediatric patient between 0 and 18 years of age suffering from a pediatric cholestatic liver disease, wherein less than 10% of the ASBTI is systemically absorbed, and wherein the ASBTI is selected from



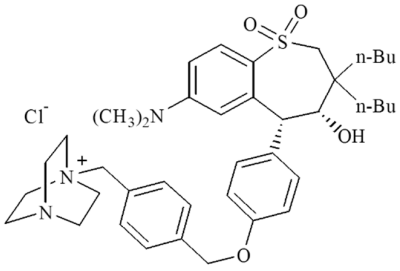
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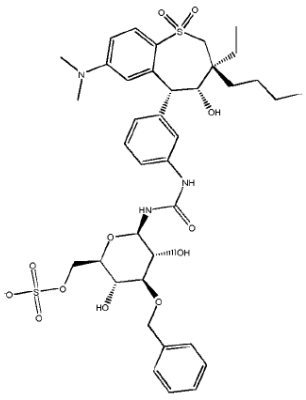
3. Use of composition comprising an Apical Sodium-dependent Bile Acid Transporter Inhibitor (ASBTI) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable diluent, excipient or carrier, in the manufacture of a medicament for treating pediatric hypercholemia in a pediatric patient between 0 and 18 years of age, wherein less than 10% of the ASBTI is systemically absorbed, and wherein the ASBTI is selected from



and  .

4. Use of a composition comprising an Apical Sodium-dependent Bile Acid Transporter Inhibitor (ASBTI) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable diluent, excipient or carrier, in the manufacture of a medicament for decreasing the level of serum bile acids or hepatic bile acids in a pediatric patient suffering from a pediatric cholestatic liver disease, wherein the pediatric patient is between 0 and 18 years of age, wherein less than 10% of the ASBTI is systemically absorbed, and wherein the ASBTI is selected from



and  .

5. The use of any one of claims 1, 2 or 4, wherein the pediatric cholestatic liver disease is progressive familial intrahepatic cholestasis (PFIC), PFIC type 1, PFIC type 2, PFIC type 3, Alagille syndrome, Dubin-Johnson Syndrome, biliary atresia, post-Kasai biliary atresia, post-liver transplantation biliary atresia, post-liver transplantation cholestasis, post-liver transplantation associated liver disease, intestinal failure associated liver disease, bile acid mediated liver injury, pediatric primary sclerosing cholangitis, 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.

6. The use of any one of claims 1, 2, 4 or 5, 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.

7. The use of any one of claims 1-6, wherein the composition decreases serum bile acid or hepatic bile acid levels in the patient by at least 20%.

8. The use of any one of claims 1-7, wherein the composition reduces xanthoma, serum lipoprotein X, liver enzymes, bilirubin, intraenterocyte bile acids/salts, or necrosis and/or damage to hepatocellular architecture.

9. The use of any one of claims 1-8, wherein the composition is a pediatric dosage form.

10. The use of claim 9, wherein the pediatric dosage form is selected from a solution, syrup, suspension, elixir, powder for reconstitution as suspension or solution, dispersible/effervescent tablet, chewable tablet, gummy candy, lollipop, freezer pops, troches, oral thin strips, orally disintegrating tablet, sachet, soft gelatin capsule, and sprinkle oral powder or granules.

11. The use of any one of claims 1-10, wherein the dosage of the ASBTI is between 1 μg/kg/day and 10 mg/kg/day.

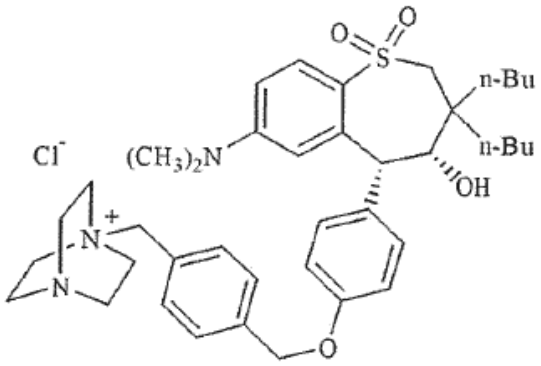
12. The use of any one of claims 1-10, wherein the dosage of the ASBTI is any dosage from 5 μg/kg/day to 1 mg/kg/day.

13. The use of any one of claims 1-10, wherein the dosage of the ASBTI comprises from 0.001 mg/kg to 10 mg/kg.

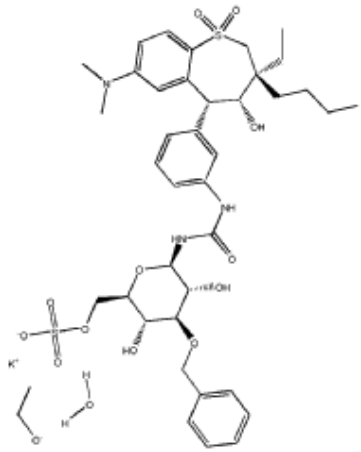
14. The use of any one of claims 1-10, wherein the dosage comprises from 0.001 mg/day to 5000 mg/day of the ASBTI.

15. The use of any one of claims 1 -14, wherein the pediatric patient is between 6 months to 12 years old.

16. The use of claim 1, wherein the compound of Formula II is

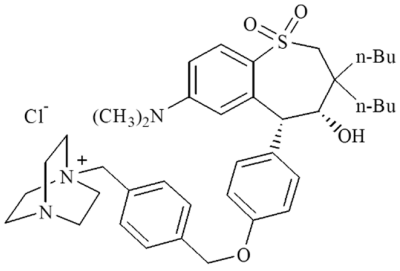


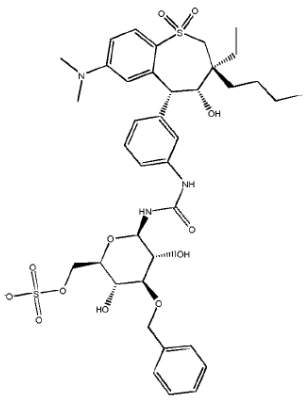
17. The use of claim 1, wherein the compound of Formula II



18. The use of any one of claims 1-17, wherein the composition further comprises a bile acid sequestrant or binder.

19. A pediatric dosage form comprising a pediatric dosage of a non-systemically absorbed Apical Sodium-dependent Bile Acid Transporter Inhibitor (ASBTI) or a pharmaceutically acceptable salt thereof, wherein the ASBTI is a compound selected from



and  .

20. The pediatric dosage form of claim 19, wherein the pediatric dosage form is selected from a solution, syrup, suspension, elixir, powder for reconstitution as suspension or solution, dispersible/effervescent tablet, chewable tablet, gummy candy, lollipop, freezer pops, troches, oral thin strips, orally disintegrating tablet, sachet, soft gelatin capsule, and sprinkle oral powder or granules.

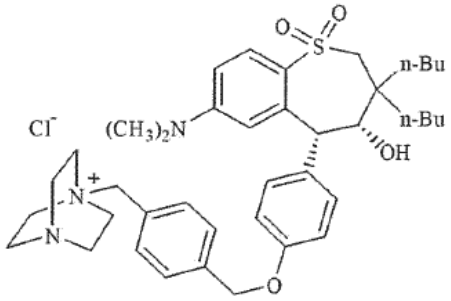
21. The pediatric dosage form of claim 19 or 20, wherein the dosage of the ASBTI is between 1 μg/kg/day and 10 mg/kg/day.

22. The pediatric dosage form of claim 19 or 20, wherein the dosage of the ASBTI is any dosage from 5 μg/kg/day to 5 mg/kg/day.

23. The pediatric dosage form of claim 19 or 20, wherein the dosage of the ASBTI is any dosage from 0.4 mg/kg/day to 5 mg/kg/day.

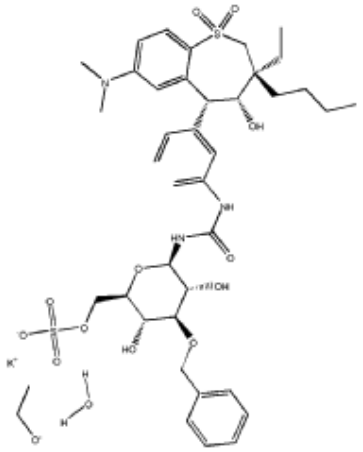
24. The pediatric dosage form of claim 19 or 20, wherein the dosage comprises between 0.1 to 20 mg of the ASBTI.

25. The pediatric dosage form of claim 19, wherein the compound of Formula II is



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26. The pediatric dosage form of claim 19, wherein the compound of Formula II



27. The pediatric dosage form of any of claim 19-26, wherein the pediatric dosage further comprises a bile acid sequestrant or binder.