BILE ACID RECYCLING INHIBITORS FOR TREATMENT OF HYPERCHOLEMIA AND CHOLESTATIC LIVER DISEASE

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, which are incorporated herein by reference in their entirety.

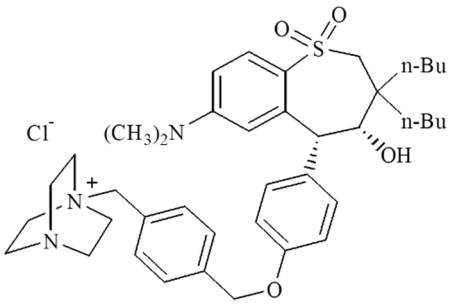
BACKGROUND OF THE INVENTION

[0002] Hypercholemia and cholestatic liver diseases are liver diseases associated with impaired bile secretion (i.e., cholestasis), associated with and often secondary to the intracellular accumulation of bile acids/salts in the hepatocyte. Hypercholemia is characterized by increased serum concentration of bile acid or bile salt. Cholestasis can be categorized clinicopathologically into two principal categories of obstructive, often extrahepatic, cholestasis, and nonobstructive, or intrahepatic, cholestasis. Nonobstructive intrahepatic cholestasis can further be classified into two principal subgroups of primary intrahepatic cholestasis that result from constitutively defective bile secretion, and secondary intrahepatic cholestasis that result from hepatocellular injury. Primary intrahepatic cholestasis includes diseases such as benign recurrent intrahepatic cholestasis, which is predominantly an adult form with similar clinical symptoms, and progressive familial intrahepatic cholestasis types 1, 2, and 3, which are diseases that affect children. Neonatal respiratory distress syndrome and lung pneumonia is often associated with intrahepatic cholestasis of pregnancy. Active treatment and prevention is limited. Currently, effective treatments for hypercholemia and cholestatic liver diseases include surgery, liver transplantation, and rarely administration of ursodiol. Effective and safe medication for hypercholemia and cholestatic liver diseases is needed.

SUMMARY

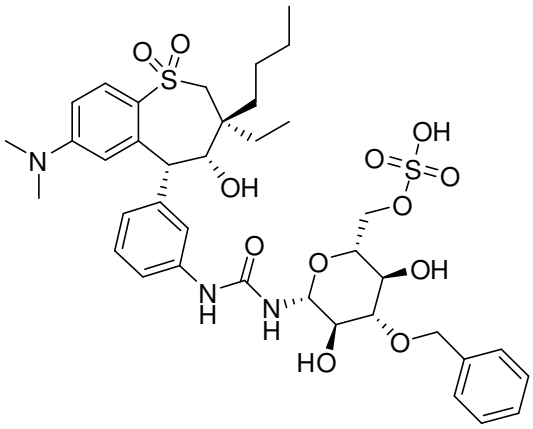
[0003] Provided herein are therapeutic compositions and methods for treating or ameliorating hypercholemia and/or cholestatic liver disease. In certain examples, provided herein are methods for treating or ameliorating hypercholemia and/or cholestatic liver disease comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of an Apical Sodium-dependent Bile Transporter Inhibitor (ASBTI) or a pharmaceutically acceptable salt thereof. In certain examples, provided herein are methods for treating or ameliorating hypercholemia and/or cholestatic liver disease comprising administering to an individual in need thereof a therapeutically effective amount of a non-systemically absorbed ASBTI or a pharmaceutically acceptable salt thereof.

[0003a] In one aspect, the present disclosure refers to the use of a therapeutically effective amount of a composition comprising a minimally absorbed Apical Sodium-dependent Bile Acid Transporter Inhibitor (ASBTI) or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment of a cholestatic liver disease or pruritis in an individual in need thereof, wherein the ASBTI is



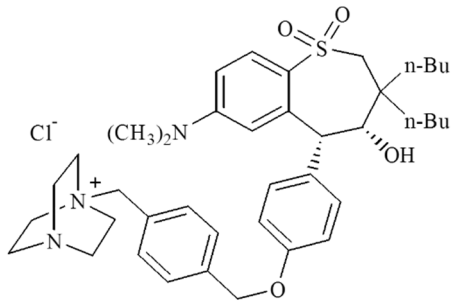
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or

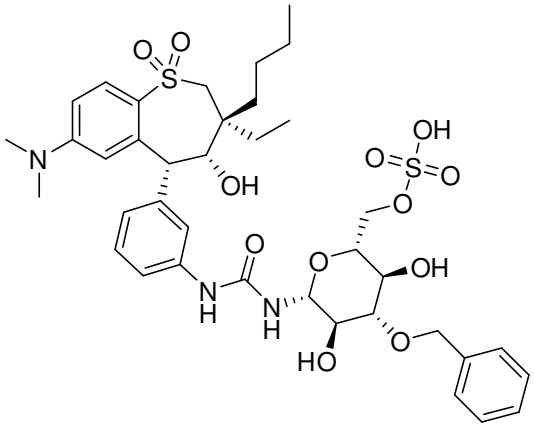


, or a pharmaceutically acceptable salt thereof.

[0003b] In another aspect, the present disclosure refers to the use of a therapeutically effective amount of a composition comprising a minimally absorbed Apical Sodium-dependent Bile Acid Transporter Inhibitor (ASBTI) or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment of a liver disease in an individual in need thereof, wherein the liver disease is progressive familial intrahepatic cholestasis (PFIC), PFIC type 1, PFIC type 2, PFIC type 3, benign recurrent intrahepatic cholestasis (BRIC), BRIC type 1, BRIC type 2, BRIC type 3, Alagille syndrome, biliary atresia, post-Kasai biliary atresia, or post-liver transplantation biliary atresia, and wherein the ASBTI is:



or



, or a pharmaceutically acceptable salt thereof.

[0004] In certain examples, provided herein are compositions comprising a non-systemically absorbed Apical Sodium-dependent Bile Acid Transporter Inhibitor (ASBTI) or a pharmaceutically acceptable salt thereof. In some examples, provided herein are compositions comprising any non-systemically absorbed ASBTI or a pharmaceutically acceptable salt thereof described herein. In some examples, provided herein are compositions comprising any non-systemically absorbed ASBTI or a pharmaceutically acceptable salt thereof and a second agent described herein.

[0005] Provided herein are therapeutic compositions and methods for treating or ameliorating pruritis. In certain examples, provided herein are methods for treating or ameliorating pruritis comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of an ASBTI or a pharmaceutically acceptable salt thereof. In certain examples, provided herein are methods for treating or ameliorating pruritis comprising administering to an individual in need thereof a therapeutically effective amount of a non-systemically absorbed ASBTI or a pharmaceutically acceptable salt thereof.

[0006] Provided herein are therapeutic compositions and methods for lowering serum bile acid levels or concentrations or hepatic bile acid levels or concentrations. In certain examples, provided herein are methods for lowering serum bile acid levels or concentrations or hepatic bile acid levels or concentrations comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of an ASBTI or a pharmaceutically acceptable salt thereof. In certain examples, provided herein are methods for lowering serum bile acid levels or concentrations or hepatic bile acid levels or concentrations comprising administering to an individual in need thereof a therapeutically effective amount of a non-systemically absorbed ASBTI or a pharmaceutically acceptable salt thereof.

[0007] In some examples, compositions and methods provided 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 provided herein or as compared to control subjects. In some examples, methods provided herein decrease serum or hepatic bile acid levels by at least 30%. In some examples, methods provided herein decrease serum or hepatic bile acid levels by at least 25%. In some examples, methods provided herein decrease serum or hepatic bile acid levels by at least 20%. In some examples, methods provided herein decrease serum or hepatic bile acid levels by at least 15%.

[0008] Provided herein are therapeutic compositions and methods for treating or ameliorating xanthoma. In certain examples, provided herein are methods for treating or ameliorating xanthoma comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of an ASBTI or a pharmaceutically acceptable salt thereof. In certain examples, provided herein are methods for treating or ameliorating xanthoma comprising administering to an individual in need thereof a therapeutically effective amount of a non-systemically absorbed ASBTI or a pharmaceutically acceptable salt thereof.

[0009] Provided herein are therapeutic compositions and methods for lowering serum lipoprotein X levels or concentrations. In certain examples, provided herein are methods for lowering serum lipoprotein X levels or concentrations comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of an ASBTI or a pharmaceutically acceptable salt thereof. In certain examples, provided herein are methods for lowering serum lipoprotein X levels or concentrations comprising administering to an individual in need thereof a therapeutically effective amount of a non-systemically absorbed ASBTI or a pharmaceutically acceptable salt thereof.

[0010] 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 an ASBTI or a pharmaceutically acceptable salt thereof. In some examples, methods comprise administering a therapeutically effective amount of a non-systemically absorbed ASBTI or a pharmaceutically acceptable salt thereof.

[0011] In certain examples, methods provided herein comprise administering compounds that inhibit the ASBT or any recuperative bile salt transporter. In certain examples, use of the compounds provided herein reduces or inhibits recycling of bile acid salts in the gastrointestinal tract. In some examples, the methods provided herein reduce intraenterocyte bile acids/salts or reduce necrosis and/or damage to intestinal or hepatocellular architecture. In certain examples, the bile transport inhibitors described herein enhance enteroendocrine peptides secretion by intestinal L-cells.

[0012] In certain examples, the methods described herein treat or ameliorate hypercholemia and/or 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 hypercholemia and/or cholestatic liver disease.

[0013] 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.

[0014] 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.

[0015] In certain examples, provided herein are methods for treating or ameliorating a liver disease comprising non-systemically administering to the distal ileum of an individual in need thereof a therapeutically effective amount of an Apical Sodium-dependent Bile Acid Transporter Inhibitor (ASBTI) or a pharmaceutically acceptable salt thereof. In some examples, provided herein are methods for treating or ameliorating a liver disease comprising non-systemically administering to the distal ileum of an individual in need thereof a therapeutically effective amount of an ASBTI or a pharmaceutically acceptable salt thereof, wherein the liver disease is hepatitis A, hepatitis B, hepatitis C, non-alcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), hemochromatosis, Wilson's disease, ischemic hepatitis, liver inflammation, liver fibrosis, or a chronic liver disease.

[0016] In certain examples, provided herein is an ASBT1 or a pharmaceutically acceptable salt thereof for use in the treatment of hypercholemia and/or cholestatic liver disease, wherein the ASBT1 is a non-systemically absorbed or is formulated to be non-systemically absorbed. In some examples, provided herein is a pharmaceutical composition for use in the treatment of hypercholemia and/or cholestatic liver disease, wherein the composition comprises an ASBT1 and a pharmaceutically acceptable excipient, wherein the ASBT1 is a non-systemically absorbed or is formulated to be non-systemically absorbed. In some examples, a composition provided herein is suitable for non-systemically administering to the distal ileum, colon, and/or rectum.

[0017] In certain examples, provided herein is an ASBT1 or a pharmaceutically acceptable salt thereof for use in the treatment of pruritis, wherein the ASBT1 is a non-systemically absorbed or is formulated to be non-systemically absorbed. In some examples, provided herein is a pharmaceutical composition for use in the treatment of pruritis, wherein the compositions comprises an ASBT1 and a pharmaceutically acceptable excipient, wherein the ASBT1 is a non-systemically absorbed or is formulated to be non-systemically absorbed. In some examples, a composition provided herein is suitable for non-systemically administering to the distal ileum, colon, and/or rectum.

[0018] In certain examples, provided herein is an ASBT1 or a pharmaceutically acceptable salt thereof for use in lowering serum bile acid concentrations or hepatic bile acid concentrations, wherein the ASBT1 is a non-systemically absorbed or is formulated to be non-systemically absorbed. In some examples, provided herein is a pharmaceutical composition for use in lowering serum bile acid concentrations or hepatic bile acid concentrations, wherein the compositions comprises an ASBT1 and a pharmaceutically acceptable excipient, wherein the ASBT1 is a non-systemically absorbed or is formulated to be non-systemically absorbed. In some examples, a composition provided herein is suitable for non-systemically administering to the distal ileum, colon, and/or rectum.

[0019] In some examples, an ASBT1 provided herein is minimally absorbed or formulated to be minimally absorbed. In some examples, an ASBT1 is non-systemically administered to the distal ileum, colon, and/or rectum of an individual in need thereof. In some examples, an ASBT1 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 ASBT1 is systemically absorbed. In a preferred example, less than 10% of the ASBT1 is systemically absorbed. In another preferred example, less than 5% of the ASBT1 is systemically absorbed. In another preferred example, less than 1% of the ASBT1 is systemically absorbed.

[0020] In one example, provided herein is a method for preventing or treating hypercholemia and/or 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 an ASBT1 or a pharmaceutically acceptable salt thereof. In one example, provided herein is a method for preventing or 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 an ASBTI or a pharmaceutically acceptable salt thereof. In one example, provided 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 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.

[0021] In certain examples, the cholestasis and/or cholestatic liver disease is obstructive cholestasis, non-obstructive cholestasis, extrahepatic cholestasis, intrahepatic cholestasis, primary intrahepatic cholestasis, secondary intrahepatic cholestasis, progressive familial intrahepatic cholestasis (PFIC), PFIC type 1, PFIC type 2, PFIC type 3, benign recurrent intrahepatic cholestasis (BRIC), BRIC type 1, BRIC type 2, BRIC type 3, total parenteral nutrition associated cholestasis, paraneoplastic cholestasis, Stauffer syndrome, intrahepatic cholestasis of pregnancy, contraceptive-associated cholestasis, drug-associated cholestasis, infection-associated cholestasis, Dubin-Johnson Syndrome, primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), gallstone disease, Alagille 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, MRP2 deficiency syndrome, or neonatal sclerosing cholangitis. In some examples, the pediatric cholestatic liver disease is a pediatric form of liver disease described herein.

[0022] In certain examples, hypercholemia and/or cholestatic liver disease is characterized by one or more symptoms selected from jaundice, pruritis, cirrhosis, 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.

[0023] In some cases, any of the methods or compositions described above reduce or ameliorate symptoms of hypercholemia and/or cholestatic liver disease and/or reduce severity of symptoms and/or reduce recurrence of hypercholemia and/or a cholestatic liver disease in a pediatric individual in need thereof. In some cases, any of the methods or compositions described above reduce or ameliorate pruritis in a pediatric individual in need thereof. In some cases, any of the methods or compositions described above lower serum bile acid concentrations or hepatic bile acid concentrations in a pediatric individual in need thereof. In some cases, for any of the methods and/or compositions described herein, 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 10 years old. In some instances, the individual is more than 10 years old. In some cases, the individual is an adult.

[0024] Provided 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 hypercholemia and/or cholestatic liver disease. In certain instances, use of the compounds provided herein reduces or inhibits recycling of bile acid salts in the gastrointestinal tract. In some examples, the methods provided herein reduce intraenterocyte bile acids/salts and/or damage to ileal or hepatocellular architecture caused by hypercholemia and/or 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.

[0025] Provided 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 pruritis. In certain instances, use of the compounds provided herein reduces or inhibits recycling of bile acid salts in the gastrointestinal tract. In some examples, the methods provided herein reduce intraenterocyte bile acids/salts and/or damage to ileal or hepatocellular architecture caused by a 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.

[0026] Provided 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 lowering serum bile acid concentrations. In certain instances, use of the compounds provided herein reduces or inhibits recycling of bile acid salts in

the gastrointestinal tract. In some examples, the methods provided herein reduce intraenterocyte bile acids/salts and/or damage to ileal or hepatocellular architecture caused by a 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.

[0027] 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.

[0028] In some examples, provided herein is a method for treating or ameliorating hypercholemia and/or cholestatic liver disease comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of an ASBTI of Formula I or a pharmaceutically acceptable salt thereof. In some examples, provided herein is a method for treating or ameliorating a liver disease comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of an ASBTI of Formula I or a pharmaceutically acceptable salt thereof, wherein the liver disease is hepatitis A, hepatitis B, hepatitis C, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), hemochromatosis, Wilson's disease, ischemic hepatitis, liver inflammation, liver fibrosis, or a chronic liver disease. In some examples, provided herein is a method for treating or ameliorating pruritis comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of an ASBTI of Formula I or a pharmaceutically acceptable salt thereof. In some examples, provided herein is a method for increasing the levels of an enteroendocrine peptide or hormone in an individual suffering from hypercholemia and/or a cholestatic liver disease comprising non-systemically administering to the individual in need thereof a therapeutically effective amount of an ASBTI of Formula I or a pharmaceutically acceptable salt thereof. In some examples, provided 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 an ASBTI of Formula I or a pharmaceutically acceptable salt thereof.

[0029] In some examples, provided herein is a method for treating or ameliorating hypercholemia and/or a cholestatic liver disease comprising non-systemically administering to an individual in need thereof

a therapeutically effective amount of an ASBTI of Formula II or a pharmaceutically acceptable salt thereof. In some examples, provided herein is a method for treating or ameliorating a liver disease comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of an ASBTI of Formula II or a pharmaceutically acceptable salt thereof, wherein the liver disease is hepatitis A, hepatitis B, hepatitis C, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), hemochromatosis, Wilson's disease, ischemic hepatitis, liver inflammation, liver fibrosis, or a chronic liver disease. In some examples, provided herein is a method for treating or ameliorating pruritis comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of an ASBTI of Formula II or a pharmaceutically acceptable salt thereof. In some examples, provided herein is a method for increasing the levels of an enteroendocrine peptide or hormone in an individual suffering from hypercholemia and/or a cholestatic liver disease comprising non-systemically administering to the individual in need thereof a therapeutically effective amount of an ASBTI of Formula II or a pharmaceutically acceptable salt thereof. In some examples, provided herein is a method for lowering serum bile acid concentrations in an individual suffering from a cholestatic liver disease comprising non-systemically administering to the individual in need thereof a therapeutically effective amount of an ASBTI of Formula II or a pharmaceutically acceptable salt thereof.

[0030] In some examples, provided herein is a method for treating or ameliorating hypercholemia and/or a cholestatic liver disease comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of an ASBTI of Formula III or a pharmaceutically acceptable salt thereof. In some examples, provided herein is a method for treating or ameliorating a liver disease comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of an ASBTI of Formula III or a pharmaceutically acceptable salt thereof, wherein the liver disease is hepatitis A, hepatitis B, hepatitis C, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), hemochromatosis, Wilson's disease, ischemic hepatitis, liver inflammation, liver fibrosis, or a chronic liver disease. In some examples, provided herein is a method for treating or ameliorating pruritis comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of an ASBTI of Formula III or a pharmaceutically acceptable salt thereof. In some examples, provided herein is a method for increasing the levels of an enteroendocrine peptide or hormone in an individual suffering from hypercholemia and/or a cholestatic liver disease comprising non-systemically administering to the individual in need thereof a therapeutically effective amount of an ASBTI of Formula III or a pharmaceutically acceptable salt thereof. In some examples, provided herein is a method for lowering serum bile acid concentrations in an individual suffering from a cholestatic liver disease comprising non-systemically administering to the individual in need thereof a therapeutically effective amount of an ASBTI of Formula III or a pharmaceutically acceptable salt thereof.

[0031] In some examples, provided herein is a method for treating or ameliorating hypercholemia and/or a cholestatic liver disease comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of an ASBTI of Formula IV or a pharmaceutically acceptable salt thereof.

In some examples, provided herein is a method for treating or ameliorating a liver disease comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of an ASBTI of Formula IV or a pharmaceutically acceptable salt thereof, wherein the liver disease is hepatitis A, hepatitis B, hepatitis C, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), hemochromatosis, Wilson's disease, ischemic hepatitis, liver inflammation, liver fibrosis, or a chronic liver disease. In some examples, provided herein is a method for treating or ameliorating pruritis comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of an ASBTI of Formula IV or a pharmaceutically acceptable salt thereof. In some examples, provided herein is a method for increasing the levels of an enteroendocrine peptide or hormone in an individual suffering from hypercholemia and/or a cholestatic liver disease comprising non-systemically administering to the individual in need thereof a therapeutically effective amount of an ASBTI of Formula IV or a pharmaceutically acceptable salt thereof. In some examples, provided herein is a method for lowering serum bile acid concentrations in an individual suffering from a cholestatic liver disease comprising non-systemically administering to the individual in need thereof a therapeutically effective amount of an ASBTI of Formula IV or a pharmaceutically acceptable salt thereof.

[0032] In some examples, provided herein is a method for treating or ameliorating hypercholemia and/or a cholestatic liver disease comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of an ASBTI of Formula V or a pharmaceutically acceptable salt thereof. In some examples, provided herein is a method for treating or ameliorating a liver disease comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of an ASBTI of Formula V or a pharmaceutically acceptable salt thereof, wherein the liver disease is hepatitis A, hepatitis B, hepatitis C, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), hemochromatosis, Wilson's disease, ischemic hepatitis, liver inflammation, liver fibrosis, or a chronic liver disease. In some examples, provided herein is a method for treating or ameliorating pruritis comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of an ASBTI of Formula V or a pharmaceutically acceptable salt thereof. In some examples, provided herein is a method for increasing the levels of an enteroendocrine peptide or hormone in an individual suffering from hypercholemia and/or a cholestatic liver disease comprising non-systemically administering to the individual in need thereof a therapeutically effective amount of an ASBTI of Formula V or a pharmaceutically acceptable salt thereof. In some examples, provided herein is a method for decreasing serum bile acid concentrations in an individual suffering from a cholestatic liver disease comprising non-systemically administering to the individual in need thereof a therapeutically effective amount of an ASBTI of Formula V or a pharmaceutically acceptable salt thereof.

[0033] In some examples, provided herein is a method for treating or ameliorating hypercholemia and/or a cholestatic liver disease comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of an ASBTI of Formula VI or a pharmaceutically acceptable salt thereof. In some examples, provided herein is a method for treating or ameliorating a liver disease comprising

non-systemically administering to an individual in need thereof a therapeutically effective amount of an ASBTI of Formula VI or a pharmaceutically acceptable salt thereof, wherein the liver disease is hepatitis A, hepatitis B, hepatitis C, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), hemochromatosis, Wilson's disease, ischemic hepatitis, liver inflammation, liver fibrosis, or a chronic liver disease. In some examples, provided herein is a method for treating or ameliorating pruritis comprising non-systemically administering to an individual in need thereof a therapeutically effective amount of an ASBTI of Formula VI or a pharmaceutically acceptable salt thereof. In some examples, provided herein is a method for increasing the levels of an enteroendocrine peptide or hormone in an individual suffering from hypercholemia and/or a cholestatic liver disease comprising non-systemically administering to the individual in need thereof a therapeutically effective amount of an ASBTI of Formula VI or a pharmaceutically acceptable salt thereof. In some examples, provided herein is a method for decreasing serum bile acid concentrations in an individual suffering from a cholestatic liver disease comprising non-systemically administering to the individual in need thereof a therapeutically effective amount of an ASBTI of Formula VI or a pharmaceutically acceptable salt thereof.

[0034] 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-benzothiazepinel,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)-l-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)-l -carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-l ,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)-l'-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-l ,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-l -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-l, l-dioxo-2,3,4,5-tetrahydro-lH-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).

[0035] In some examples, an ASBTI is not 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)-l -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)-l-carboxyethyl)carbamoyl]benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; or a pharmaceutically acceptable salt thereof.

[0036] In certain examples, methods provided 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 provided 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 some examples, the dosage of an ASBTI is between about 1 μg/kg/day and about 10 mg/kg/day. In some examples, the dosage of an ASBTI is between about 5 μg/kg/day and about 1 mg/kg/day. In some examples, the dosage of an ASBTI is between about 10 μg/kg/day and about 300 μg/kg/day. In some examples, the dosage of an ASBTI is any dosage from about 14 μg/kg/day and about 280 μg/kg/day. In some examples, the dosage of an ASBTI is any dosage from about 14 μg/kg/day and about 140 μg/kg/day. In some examples, the dosage of an ASBTI is between about 5 μg/kg/day and about 200 μg/kg/day. In some examples, the dosage of an ASBTI is between about 10 μg/kg/day and about 200 μg/kg/day. In some examples, the dosage of an ASBTI is between about 10 μg/kg/day and about 175 μg/kg/day. In some examples, the dosage of an ASBTI is between about 10 μg/kg/day and about 150 μg/kg/day. In some examples, the dosage of an ASBTI is between about 10 μg/kg/day and about 140 μg/kg/day. In some examples, the dosage of an ASBTI is between about 25 μg/kg/day and about 140 μg/kg/day. In some examples, the dosage of an ASBTI is between about 50 μg/kg/day and about 140 μg/kg/day. In some examples, the dosage of an ASBTI is between about 70 μg/kg/day and about 140 μg/kg/day. In some examples, the dosage of an ASBTI is between about 10 μg/kg/day and about 100 μg/kg/day. In some examples, the dosage of an ASBTI is 10 μg/kg/day. In some examples, the dosage of an ASBTI is 20 μg/kg/day. In some examples, the dosage of an ASBTI is 30 μg/kg/day. In some examples, the dosage of an ASBTI is 35 μg/kg/day. In some examples, the dosage of an ASBTI is 40 μg/kg/day. In some examples, the dosage of an ASBTI is 50 μg/kg/day. In some examples, the dosage of an ASBTI is 60 μg/kg/day. In some examples, the dosage of an ASBTI is 70 μg/kg/day. In some examples, the dosage of an ASBTI is 80 μg/kg/day. In some examples, the dosage of an ASBTI is 90 μg/kg/day. In some examples, the dosage of an ASBTI is 100 μg/kg/day. In some examples, the dosage of an ASBTI is 110 μg/kg/day. In some examples, the dosage of an ASBTI is 120 μg/kg/day. In some examples, the dosage of an ASBTI is 130 μg/kg/day. In some examples, the dosage of an ASBTI is 140 μg/kg/day. In some examples, the dosage of an ASBTI is 150 μg/kg/day. In some examples, the dosage of an ASBTI is 175 μg/kg/day.

[0038] In some examples, provided herein are dosages of anASBTI between 14 μg/kg/day and 140 μg/kg/day, or between 14 μg/kg/day and 280 μg/kg/day.

[0039] In some examples, the dosage of an ASBTI is between about 0.5 mg/day and about 40 mg/day. In some examples, the dosage of an ASBTI is between about 0.5 mg/day and about 30 mg/day. In some examples, the dosage of an ASBTI is between about 1 mg/day and about 20 mg/day. In some examples, the dosage of an ASBTI is between about 1 mg/day and about 10 mg/day. In some examples, the dosage of an ASBTI is between about 1 mg/day and about 5 mg/day. In some examples, the dosage of an ASBTI is 1 mg/day. In some examples, the dosage of an ASBTI is 5 mg/day. In some examples, the dosage of an ASBTI is 10 mg/day. In some examples, the dosage of an ASBTI is 20 mg/day. In some examples, the dosage of an ASBTI is between 0.5 mg/day and 5 mg/day. In some examples, the dosage of an ASBTI is between 0.5 mg/day and 4.5 mg/day. In some examples, the dosage of an ASBTI is between 0.5 mg/day and 4 mg/day. In some examples, the

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

[0040] In some examples, the dosage form comprises 0.5 mg of the ASBTI. In some examples, the dosage form comprises 1 mg of the ASBTI. In some examples, the dosage form comprises 2.5 mg of the ASBTI. In some examples, the dosage form comprises 5 mg of the ASBTI. In some examples, the dosage form comprises 10 mg of the ASBTI. In some examples, the dosage form comprises 20 mg of the ASBTI.

[0041] In certain examples, the dosage of an ASBTI is given once a day. In some examples, the dosage of an ASBTI is given q.d. In some examples, the dosage of an ASBTI is given once a day in the morning. In some examples, the dosage of an ASBTI is given once a day at noon. In some examples, the dosage of an ASBTI is given once a day in the evening or night. In some examples, the dosage of an ASBTI is given twice a day. In some examples, the dosage of an ASBTI is given b.i.d. In some examples, the dosage of an ASBTI is given twice a day, in the morning and noon. In some examples, the dosage of an ASBTI is given twice a day, in the morning and evening. In some examples, the dosage of an ASBTI is given twice a day, in the morning and night. In some examples, the dosage of an ASBTI is given twice a day, at noon and in the evening. In some examples, the dosage of an ASBTI is given twice a day, at noon and in the night. In some examples, the dosage of an ASBTI is given three times a day. In some examples, the dosage of an ASBTI is given t.i.d. In some examples, the dosage of an ASBTI is given four times a day. In some examples, the dosage of an ASBTI is given q.i.d. In some examples, the dosage of an ASBTI is given every four hours. In some examples, the dosage of an ASBTI is given q.q.h. In some examples, the dosage of an ASBTI is given every other day. In some

examples, the dosage of an ASBTI is given q.o.d. In some examples, the dosage of an ASBTI is given three times a week. In some examples, the dosage of an ASBTI is given t.i.w.

[0042] Provided in certain examples herein are methods and dosage forms (e.g., oral or rectal dosage form) for use in the treatment of hypercholemia and/or a cholestatic liver disease and/or pruritis, or for use in lowering serum bile acid or hepatic bile acid levels comprising a therapeutically effective amount of an ASBTI, or a pharmaceutically acceptable salt thereof, and a carrier. In some examples, methods comprise 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, methods comprise rectally administering a therapeutically effective amount of a minimally absorbed ASBTI, or a pharmaceutically acceptable salt thereof, to an individual in need thereof. In specific examples, the dosage form is an enteric formulation, an ileal-pH sensitive release formulation, or a suppository or other suitable form.

[0043] In some examples, a composition for use in the treatment of hypercholemia and/or a 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 examples, the composition comprises an absorption inhibitor. In some cases an absorption inhibitor is a mucoadhesive agent (e.g., a mucoadhesive polymer). In certain examples, the mucoadhesive agent is selected from methyl cellulose, polycarbophil, polyvinylpyrrolidone, sodium carboxymethyl cellulose, and combinations thereof. In some examples, the enteroendocrine peptide secretion enhancing agent is covalently linked to the absorption inhibitor. In certain examples, the pharmaceutical composition comprises an enteric coating. In some examples, a composition for use in treatment of cholestasis, a cholestatic liver disease or pruritis described above comprises a carrier. In certain examples, the carrier is a rectally suitable carrier. In certain examples, any pharmaceutical composition described herein is formulated as a suppository, an enema solution, a rectal foam, or a rectal gel. In some examples, any pharmaceutical composition described herein comprises an orally suitable carrier.

[0044] In some examples, provided herein is a pharmaceutical composition formulated for non-systemic ileal, rectal or colonic delivery of the ASBTI.

[0045] 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 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 hypercholemia and/or a cholestatic liver disease or elevated serum or hepatic bile acid 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 hypercholemia and/or by a cholestatic liver disease in an individual suffering from a cholestatic liver disease.

[0046] In some examples, the methods described above further comprise administration of a second agent selected from ursodiol, norursodiol, 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.

[0047] In some examples, provided herein are methods for the treatment of hypercholemia and/or a cholestatic liver disease comprising administration of a therapeutically effective amount of a combination of an ASBTI and ursodiol to an individual in need thereof. In some examples, provided herein are methods for the treatment of hypercholemia and/or a 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 examples, an ASBTI is administered in combination with one or more agent selected from the group consisting of ursodiol, ursodeoxycholic acid, chenodeoxycholic acid, cholic acid, taurocholic acid, ursocholic acid, glycocholic acid, glycodeoxycholic acid, taurodeoxycholic acid, taurocholate, glycochenodeoxycholic acid, tauroursodeoxycholic acid, 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, a resin or sequestrant for absorbing bile acids.

[0048] In some examples, the ASBTI is administered orally. In some 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 examples, the ASBTI is administered as an enterically coated formulation. In some examples, oral delivery of an ASBTI provided 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 disclosure. Suitable enteric coatings include cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methacrylic acid methyl ester.

[0049] In some examples of the methods described above, the ASBTI is administered before ingestion of food. In some examples of the methods described above, the ASBTI is administered with or after ingestion of food.

[0050] In some examples, the methods provided herein further comprise administration of vitamin supplements to compensate for reduced digestion of vitamins, in particular fat-soluble vitamins, in an individual with hypercholemia and/or a cholestatic liver disease. In some examples, the vitamin supplements comprise fat-soluble vitamins. In some examples, the fat-soluble vitamins are vitamin A, D, E, or K.

[0051] In some examples, the methods provided herein further comprise administration of vitamin supplements to compensate for reduced digestion of vitamins, in particular fat-soluble vitamins, in an individual suffering from pruritis. In some examples, the vitamin supplements comprise fat-soluble vitamins. In some examples, the fat-soluble vitamins are vitamin A, D, E, or K.

[0052] In some examples, the methods provided herein further comprise administration of vitamin supplements to compensate for reduced digestion of vitamins, in particular fat-soluble vitamins, in an individual with elevated serum bile acid concentrations. In some examples, the vitamin supplements comprise fat-soluble vitamins. In some examples, the fat-soluble vitamins are vitamin A, D, E, or K.

[0053] In some examples, the methods and compositions provided herein further comprise administration of a bile acid sequestrant or binder for reducing gastrointestinal side effects. In some 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 examples, a labile bile acid sequestrant provided herein releases a bile acid in the colon or the rectum of a human. In some examples, a labile bile acid sequestrant provided herein does not sequester a bile acid for excretion or elimination in feces. In some examples, a labile bile acid sequestrant provided herein is a non-systemic labile bile acid sequestrant. In some 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 examples, the labile bile acid sequestrant is lignin or a modified lignin. In some examples, the labile bile acid sequestrant is a polycationic polymer or copolymer. In certain 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.

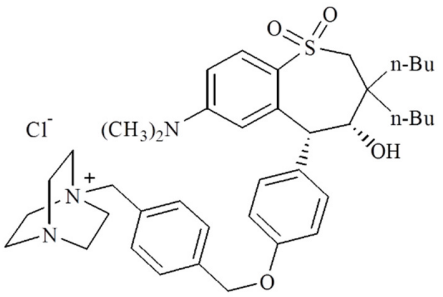
[0054] In some examples, the methods provided herein further comprise partial external biliary diversion (PEBD).

[0055] Provided 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.

CLAIMS

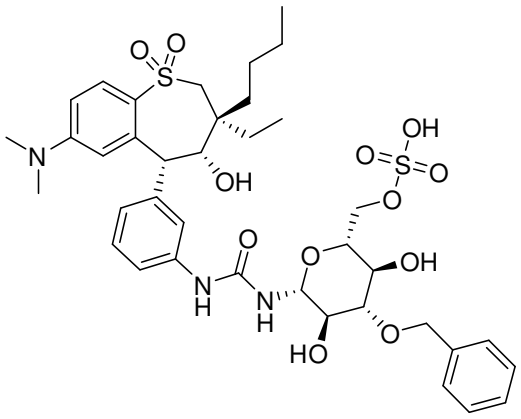
WHAT IS CLAIMED IS:

1. Use of a therapeutically effective amount of a composition comprising a minimally absorbed Apical Sodium-dependent Bile Acid Transporter Inhibitor (ASBTI) or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment of a cholestatic liver disease or pruritis in an individual in need thereof, wherein the ASBTI is



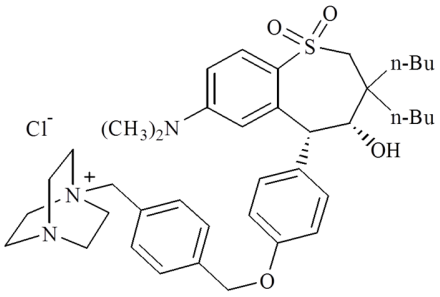
,

or



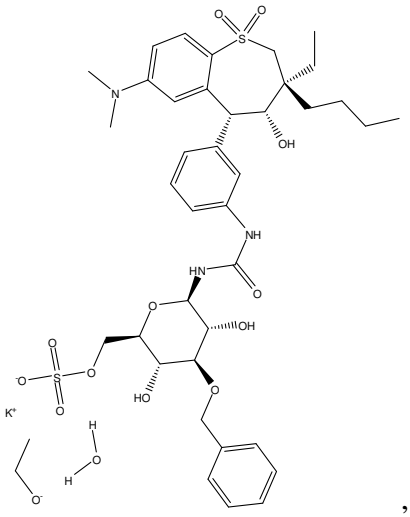
, or a pharmaceutically acceptable salt thereof.

2. The use in claim 1, wherein the compound is



, or an alternative pharmaceutically acceptable salt thereof.

3. The use in claim 1, wherein the compound is



, or an alternative pharmaceutically acceptable salt thereof.

4. The use in claim 1, wherein the ASBTI decreases the levels of serum bile acids or hepatic bile acids, reduces bilirubin, reduces liver enzymes, lowers intraenterocyte bile acids/salts, or reduces necrosis and/or damage to hepatocellular architecture.

5. The use in claim 1, wherein the ASBTI decreases elevated levels of lipoprotein X; elevated levels of AP (alkaline phosphatase); elevated levels of LAP (leukocyte alkaline phosphatase); elevated levels of gamma GT (gamma-glutamyl transpeptidase); elevated levels of 5'-nucleotidase; pruritus; elevated serum concentration of conjugated bilirubin; elevated serum concentrations of nonconjugated bilirubin or delta bilirubin; and presence of xanthomas.

6. The use in claim 1, wherein the cholestatic liver disease is an obstructive cholestasis, non-obstructive cholestasis, extrahepatic cholestasis, intrahepatic cholestasis, primary intrahepatic cholestasis, secondary intrahepatic cholestasis, progressive familial intrahepatic cholestasis (PFIC), PFIC type 1, PFIC type 2, PFIC type 3, benign recurrent intrahepatic cholestasis (BRIC), BRIC type 1, BRIC type 2, BRIC type 3, total parenteral nutrition associated cholestasis, paraneoplastic cholestasis, Stauffer syndrome, intrahepatic cholestasis of pregnancy, contraceptive-associated cholestasis, drug-associated cholestasis, infection-associated cholestasis, Dubin-Johnson Syndrome, primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), gallstone disease, 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, or MRP2 deficiency syndrome.

7. The use in claim 1, wherein the cholestatic liver disease is intrahepatic cholestasis of pregnancy (ICP).

8. The use in claim 7, wherein the ICP is in the third trimester of pregnancy.

9. The use in claim 7, wherein the ICP is characterized by one or more of pruritis, biochemical cholestasis, or cholestatic liver disease.

10. The use in claim 7, wherein the individual has a genetic predisposition to ICP.

11. The use in claim 10, wherein the genetic predisposition to ICP comprises a heterogenous state for an MDR3 gene defect.

12. The use in claim 1, wherein the cholestatic liver disease is primary sclerosing cholangitis (PSC).

13. The use in claim 1, wherein the 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 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.

14. The use in claim 1, wherein less than 10% of the ASBTI is systemically absorbed.

15. The use in claim 1, further comprises a second agent selected from ursodeoxycholic acid, chenodeoxycholic acid, cholic acid, taurocholic acid, ursocholic acid, glycocholic acid, glycodeoxycholic acid, taurodeoxycholic acid, taurocholate, glycochenodeoxycholic acid, and tauroursodeoxycholic acid.

16. The use in claim 1, wherein the ASBTI is to be administered before ingestion of food, optionally wherein the ASBTI is administered less than about 60 minutes or less than about 30 minutes before ingestion of food.

17. The use in claim 1, wherein the ASBTI is to be administered orally.

18. The use in claim 1, wherein the ASBTI is to be administered as an ileal-pH sensitive release or an enterically coated formulation.

19. The use in claim 1, further comprising a vitamin supplement.

20. The use in claim 19, wherein the vitamin supplement comprises a fat-soluble vitamin.

21. The use in claim 20, wherein the fat-soluble vitamin is vitamin A, D, E, or K.

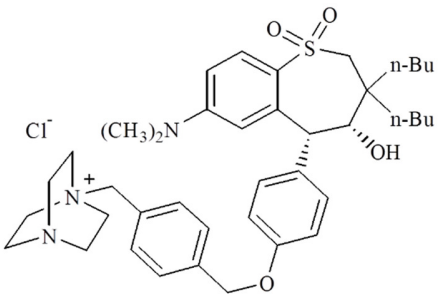
22. The use in claim 1, further comprising an agent selected from the group consisting of cholestyramine, antihistamine, rifampin, naloxone, Phenobarbital, dronabinol, methotrexate, corticosteroid, cyclosporine, and colchicines.

23. The use in claim 1, further comprising the use of partial external biliary diversion (PEBD).

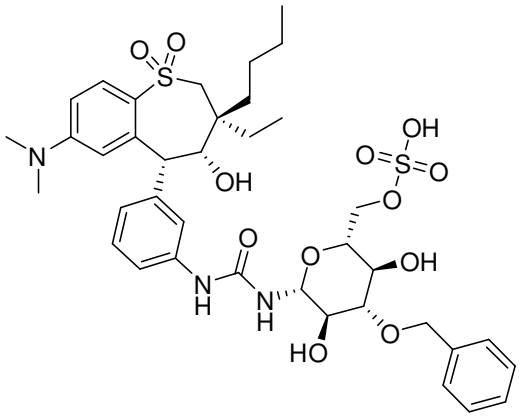
24. The use in claim 1, wherein the individual in need thereof is nonresponsive to ursodiol.

25. The use in claim 1, further comprising a bile acid sequestrant or binder.

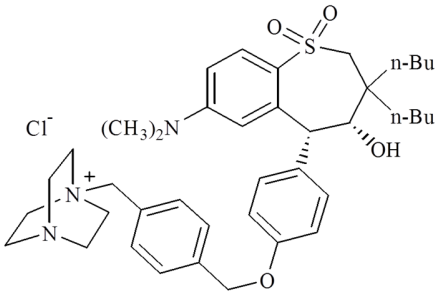
26. Use of a therapeutically effective amount of a composition comprising a minimally absorbed Apical Sodium-dependent Bile Acid Transporter Inhibitor (ASBTI) or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment of a liver disease in an individual in need thereof, wherein the liver disease is progressive familial intrahepatic cholestasis (PFIC), PFIC type 1, PFIC type 2, PFIC type 3, benign recurrent intrahepatic cholestasis (BRIC), BRIC type 1, BRIC type 2, BRIC type 3, Alagille syndrome, biliary atresia, post-Kasai biliary atresia, or post-liver transplantation biliary atresia, and wherein the ASBTI is:



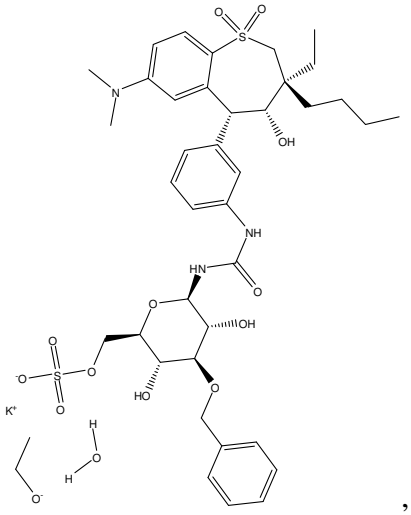
or


, or a pharmaceutically acceptable salt thereof.

27. The use in claim 26, wherein the compound is


, or an alternative pharmaceutically acceptable salt thereof.

28. The use in claim 26, wherein the compound is


, or an alternative pharmaceutically acceptable salt thereof.

29. The use in claim 26, wherein less than 10% of the ASBTI is systemically absorbed.

30. The use in claim 26, further comprises a second agent selected from ursodeoxycholic acid, chenodeoxycholic acid, cholic acid, taurocholic acid, ursocholic acid, glycocholic acid, glycodeoxycholic acid, taurodeoxycholic acid, taurocholate, glycochenodeoxycholic acid, and tauroursodeoxycholic acid.

31. The use in claim 26, wherein the ASBTI is administered before ingestion of food, optionally wherein the ASBTI is administered less than about 60 minutes or less than about 30 minutes before ingestion of food.

32. The use in claim 26, wherein the ASBTI is to be administered orally.

33. The use in claim 26, wherein the ASBTI is to be administered as an ileal-pH sensitive release or an enterically coated formulation.

34. The use in claim 26, further comprising a vitamin supplement.

35. The use in claim 34, wherein the vitamin supplement comprises a fat-soluble vitamin.

36. The use in claim 35, wherein the fat-soluble vitamin is vitamin A, D, E, or K.

37. The use in claim 26, further comprising an agent selected from the group consisting of cholestyramine, antihistamine, rifampin, naloxone, Phenobarbital, dronabinol, methotrexate, corticosteroid, cyclosporine, and colchicines.

38. The use in claim 26, wherein the individual in need thereof is nonresponsive to ursodiol.

39. The use in claim 26, further comprising a bile acid sequestrant or binder.

40. The use in claim 26, wherein the liver disease is progressive familial intrahepatic cholestasis (PFIC).

41. The use in claim 26, wherein the liver disease is Alagille syndrome.

42. The use in claim 1, wherein the ASBTI decreases serum or hepatic bile acid levels in the individual by at least about 30% as compared to the levels prior to administration of the ASBTI.

43. The use in claim 1, wherein the ASBTI decreases serum or hepatic bile acid levels in the individual by at least about 40% as compared to the levels prior to administration of the ASBTI.

44. The use in claim 1, wherein the ASBTI decreases serum or hepatic bile acid levels in the individual by at least about 50% as compared to the levels prior to administration of the ASBTI.

45. The use in claim 26, wherein the ASBTI decreases serum or hepatic bile acid levels in the individual by at least about 30% as compared to the levels prior to administration of the ASBTI.

46. The use in claim 26, wherein the ASBTI decreases serum or hepatic bile acid levels in the individual by at least about 40% as compared to the levels prior to administration of the ASBTI.

47. The use in claim 26, wherein the ASBTI decreases serum or hepatic bile acid levels in the individual by at least about 50% as compared to the levels prior to administration of the ASBTI.

48. The use of any of claims 1-47, wherein the ASBTI is to be administered at a dosage between about 1 µg/kg/day and about 10 mg/kg/day.

49. The use of claim 48, wherein the ASBTI is to be administered at a dosage from about 5 µg/kg/day to about 1 mg/kg/day.

50. The use of claim 48, wherein the ASBTI is to be administered at a dosage from about 10 µg/kg/day to about 300 µg/kg/day.

51. The use of any of claims 1-50, wherein the ASBTI is to be administered at a dosage comprising from about 0.1 mg/day to about 40 mg/day of the ASBTI.

52. The use of any of claims 1-51, wherein the individual has a defective BSEP expression and/or function.

53. The use of any of claims 1-52, wherein the individual has a mutation in ABCB11 gene.

54. The use of any of claims 1-52, wherein the individual has a mutation in ABCB4 gene.