[0004] Pediatric cholestatic liver diseases affect a small percentage of children, but therapy results in significant healthcare costs each year. Currently, many of the pediatric cholestatic liver diseases require invasive and costly treatments such as liver transplantation and surgery. An effective and less invasive treatment at a dosing with minimal gastrointestinal adverse effects that is suitable for the pediatric population is not available.

[0005] In recent years apical sodium-dependent bile acid transporter inhibitors (ASBTIs) have evolved as an important novel class of therapeutic agents capable of reducing serum and/or hepatic bile acids and thus reducing cholestasis. There exists a further urgent need to reduce ASBTI adverse effects and/or to develop methods of treating cholestasis and cholestatic liver disease with reduced adverse effects.

SUMMARY OF THE DISCLOSURE

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

[0007] In one example, the present disclosure provides a method for reducing, minimizing, preventing, ameliorating, or eliminating one or more side effects associated with administration of an apical sodium-dependent bile acid transporter inhibitor (ASBTI) in a subject in need thereof, the method comprising administering a therapeutically effective amount of the ASBTI to the subject before ingestion of food.

[0007a] In one aspect, the present disclosure provides a use of an apical sodium-dependent bile acid transporter inhibitor (ASBTI) in the manufacture of a medicament for reducing, minimizing, preventing, ameliorating, or eliminating one or more side effects associated with administration of the ASBTI in a subject in need thereof, the use comprising the ASBTI to be administered to the subject before ingestion of food.

[0008] In certain examples, the one or more side effects associated with administration of the ASBTI is reduced, minimized, prevented, ameliorated or eliminated as compared to the side effects when the ASBTI is administered after ingestion of food, at the same time as food, or mixed with food.

[0009] In another example, the present disclosure provides a method of improving gastrointestinal (GI) tolerability of an ASBTI in a subject in need thereof, the method comprising administering a therapeutically effective amount of the ASBTI to the subject before ingestion of food.

[0009a] In another aspect, the present disclosure provides a use of an ASBTI in the manufacture of a medicament for improving gastrointestinal (GI) tolerability of the ASBTI in a subject in need thereof, the use comprising the ASBTI to be administered to the subject before ingestion of food.

[0010] In some examples, the improvement of GI tolerability comprises a reduction, minimization, prevention, amelioration, or elimination of one or more GI adverse events.

[0011] In some examples, the improvement of GI tolerability comprises a reduction, minimization, prevention, amelioration, or elimination of one or more of diarrhea, loose stools, nausea, abdominal pain, and anorectal discomfort.

[0012] In some examples, the GI tolerability is improved as compared to the GI tolerability when the ASBTI is administered at mealtime or immediately after food intake.

[0013] In some examples, the GI tolerability is improved by at least 10% as compared to the GI tolerability when the ASBTI is administered at mealtime or immediately after food intake.

[0014] In some examples, the GI tolerability is improved by at least 20% as compared to the GI tolerability when the ASBTI is administered at mealtime or immediately after food intake.

[0015] In some examples, the GI tolerability is improved by at least 50% as compared to the GI tolerability when the ASBTI is administered at mealtime or immediately after food intake.

[0016] In one example, the present disclosure provides method of treating cholestatic liver disease in a subject in need thereof, the method comprising administering a therapeutically effective amount of an ASBTI to the subject before ingestion of food, wherein the subject experiences a reduction in frequency and/or severity of one or more side effects associated with the administration of the ASBTI.

[0016a] In another aspect, the present disclosure provides a use of an ASBTI in the manufacture of a medicament for treating cholestatic liver disease in a subject in need thereof, the use comprising the ASBTI to be administered to the subject before ingestion of food, wherein the subject experiences a reduction in frequency and/or severity of one or more side effects associated with the administration of the ASBTI.

[0017] In certain examples, the frequency and/or severity of side effects is reduced as compared to the side effects when the ASBTI is administered after ingestion of food, at the same time as food, or mixed with food.

[0018] In certain examples, the cholestatic liver disease is a pediatric cholestatic liver disease. In certain examples, the cholestatic liver disease is an adult cholestatic liver disease. In certain examples, the cholestatic liver disease is 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 certain examples, the cholestatic liver disease is Alagille syndrome, PFIC, BRIC, PSC, PBC, or biliary atresia.

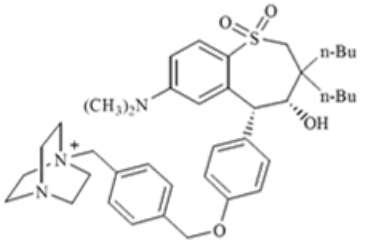
[0019] In certain examples, the ASBTI is administered to the subject in a fasted state. In certain examples, the ASBTI is administered less than about 60 minutes before ingestion of

food. In certain examples, the ASBTI is administered less than about 30 minutes before ingestion of food. In certain examples, the ASBTI is administered immediately prior to the ingestion of food. In certain examples, the ASBTI is administered at least 4 hours after the last meal.

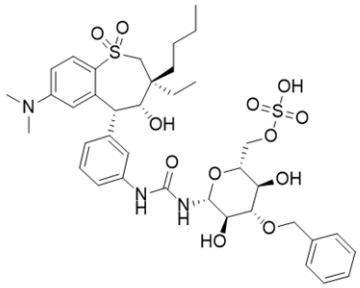
[0020] In certain examples, the ASBTI is administered once daily. In certain examples, the ASBTI is administered twice daily.

[0021] In certain examples, the ASBTI is administered in an amount of about 0.1 mg to about 100 mg per dose. In certain examples, the ASBTI is administered in an amount of about 10 mg to about 100 mg per dose. In certain examples, the ASBTI is administered in an amount of about 20 mg to about 80 mg per dose. In certain examples, the ASBTI is administered in an amount of about 100 µg/kg/day to 1400 µg/kg/day. In certain examples, the ASBTI is administered in an amount of about 400 µg/kg/day to 800 µg/kg/day.

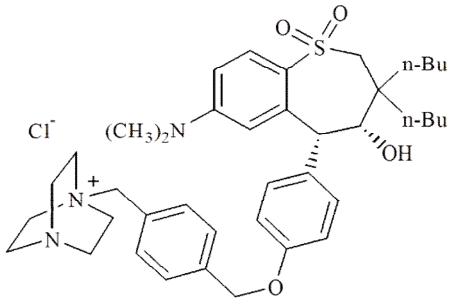
[0022] In certain examples, the ASBTI is selected from



(maralixibat) and



(volixibat) or a pharmaceutically acceptable salt thereof. In certain examples, the ASBTI is



(maralixibat chloride). In certain examples, the ASBTI is volixibat or a pharmaceutically acceptable salt thereof. In certain examples, the ASBTI is volixibat potassium.

[0023] In certain examples, the subject has not ingested food for about 0.5 to about 16 hours before the administration of the ASBTI.

[0024] In certain examples, the subject is a pediatric subject. In certain examples, the pediatric subject is 0 to 18 years of age.

[0025] In certain examples, the ASBTI is administered orally.

[0026] In certain examples, less than 10% of the ASBTI is systemically absorbed. In certain examples, less than 30% of the ASBTI is systemically absorbed.

BRIEF DESCRIPTION OF THE DRAWINGS

[0027] **Figure 1** depicts study designs, drugs (MRX = maralixibat, VLX = volixibat), doses and at mealtime/fasted timelines for certain embodiments according to the disclosure. *Fasting was started ≥10-12 hours before MRX dosing. ǂPatients were randomized 1:1 to two cohorts and received sequentially fasted then at mealtime dosing, or at mealtime then fasted dosing.

[0028] **Figure 2** is pie charts showing the proportion of healthy participants who experienced gastrointestinal (GI) treatment-emergent adverse events (AEs) following ASBTI administration at mealtime versus in the fasted state for each of the three studies.

[0029] **Figure 3** shows the effect of maralixibat (MRX) on fecal bile acid (fBA) excretion in dogs: study drug, and dosing/mealtime schedule.

[0030] **Figure 4** is a bar graph of the effect of maralixibat (MRX) on fecal bile acid (fBA) in dogs: change in fBA excretion from pre-treatment to day 7.

DETAILED DESCRIPTION

[0031] Detailed embodiments of the present invention are disclosed herein; however, it is to be understood that the disclosed embodiments are merely illustrative of the invention that may be embodied in various forms. In addition, each of the examples given in connection with the various embodiments of the invention is intended to be illustrative, and not restrictive. Therefore, specific structural and functional details disclosed herein are not to be interpreted as limiting, but merely as a representative basis for teaching one skilled in the art to variously employ the present invention.

[0032] 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