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.

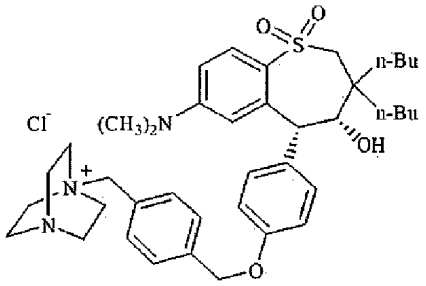
BACKGROUND OF THE INVENTION

[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.

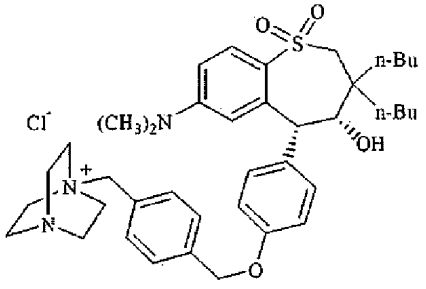
SUMMARY OF THE INVENTION

[0003a] In one aspect, there is provided use of a composition comprising an Apical Sodium-dependent Bile Acid Transporter Inhibitor (ASBTI) which is



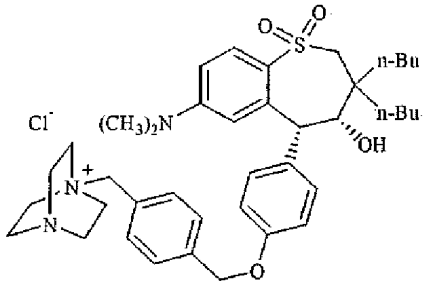
or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a pediatric cholestatic liver disease in a human pediatric patient aged between 0 and 18 years of age.

[0003b] In one aspect, there is provided use of a composition comprising an Apical Sodium-dependent Bile Acid Transporter Inhibitor (ASBTI) which is



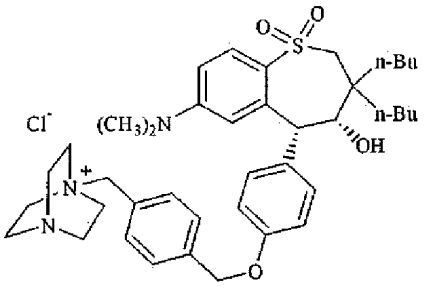
or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of pruritis in a human pediatric patient aged between 0 and 18 years of age.

[0003c] In one aspect, there is provided use of a composition comprising an Apical Sodium-dependent Bile Acid Transporter Inhibitor (ASBTI) which is



or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of hypercholemia in a human pediatric patient aged between 0 and 18 years of age.

[003d] In one aspect, there is provided use of a composition comprising an Apical Sodium-dependent Bile Acid Transporter Inhibitor (ASBTI) which is

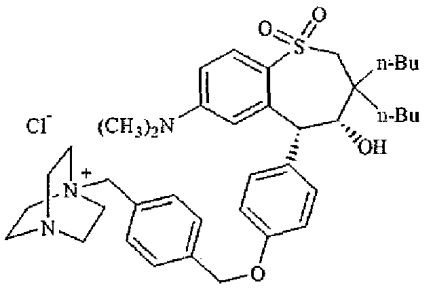


or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for decreasing the level of serum bile acids in a human pediatric patient aged between 0 and 18 years of age.

[0004] Provided herein are therapeutic compositions and methods for treating or ameliorating a pediatric cholestatic liver disease or pediatric cholestasis. In certain embodiments, provided 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 embodiments, provided 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 embodiments, provided 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 embodiments, provided 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.

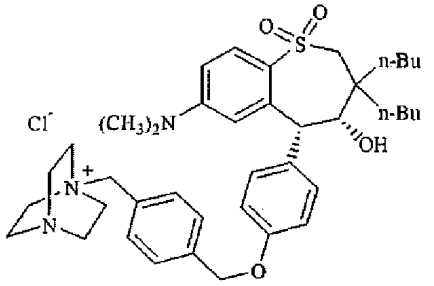
CLAIMS

1. Use of a composition comprising an Apical Sodium-dependent Bile Acid Transporter Inhibitor (ASBTI) which is



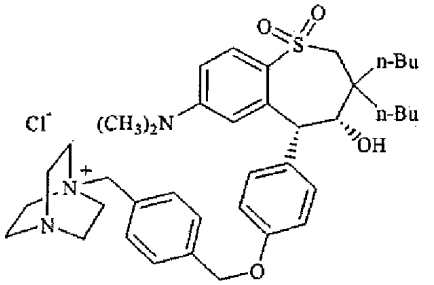
or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a pediatric cholestatic liver disease in a human pediatric patient aged between 0 and 18 years of age.

2. Use of a composition comprising an Apical Sodium-dependent Bile Acid Transporter Inhibitor (ASBTI) which is



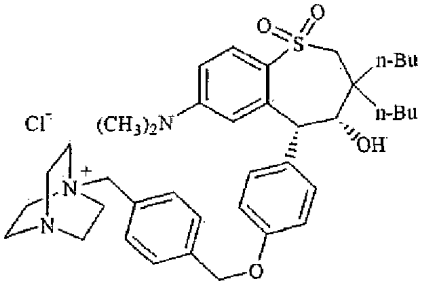
or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of pruritis in a human pediatric patient aged between 0 and 18 years of age.

3. Use of a composition comprising an Apical Sodium-dependent Bile Acid Transporter Inhibitor (ASBTI) which is



or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of hypercholemia in a human pediatric patient aged between 0 and 18 years of age.

4. Use of a composition comprising an Apical Sodium-dependent Bile Acid Transporter Inhibitor (ASBTI) which is



or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for decreasing the level of serum bile acids in a human pediatric patient aged between 0 and 18 years of age.

5. The use of any one of claims 1-4, wherein the composition decreases at least 20% of serum bile acid or hepatic bile acid levels in the patient.

6. The use of any one of claims 1-5, wherein the composition decreases at least 30% of serum bile acid or hepatic bile acid levels in the patient.

7. The use of any one of claims 1-6, wherein the composition decreases at least 40% of serum bile acid or hepatic bile acid levels in the patient.

8. The use of any one of claims 1-7, wherein the composition decreases at least 50% of serum bile acid or hepatic bile acid levels in the patient.

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

10. The use of any one of claims 1-9, wherein the composition is a dosage form appropriate for treating a human pediatric patient.

11. The use of claim 10, wherein the 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.

12. The use of any one of claims 1-11, wherein the dosage of the ASBTI is between 10 μg/kg/day and 300 μg/kg/day.

13. The use of any one of claims 1-11, wherein the dosage of the ASBTI is any dosage from 14μg/kg/day to 280 μg/kg/day.

14. The use of any one of claims 1-11, wherein the dosage of the ASBTI is any dosage from 14μg/kg/day to 140 μg/kg/day.

15. The use of any one of claims 1-11, wherein the dosage comprises between 0.1 to 20 mg of the ASBTI.

16. The use of any one of claims 1-15, 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.

17. The use of any one of claims 1-16, wherein the pediatric cholestatic liver disease is progressive familial intrahepatic cholestasis (PFIC), PFIC type 1, PFIC type 2, or PFIC type 3.

18. The use of any one of claims 1-16, wherein the pediatric cholestatic liver disease is Alagille syndrome.

19. The use of any one of claims 1-18, wherein the 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 renal failure.

20. The use of any one of claims 1-19, wherein the human pediatric patient is between 6 months to 12 years old.

21. The use of any one of claims 1-20, wherein less than 10% of the ASBTI is systemically absorbed.

22. The use of any one of claims 1-21, wherein the composition further comprises a bile acid sequestrant or binder.