

diseases require invasive and costly treatments such as liver transplantation and surgery. There is a need for an effective, less invasive, transplant-free survival (TFS) treatment that provides long-term event-free survival (EFS).

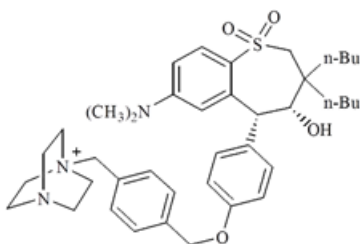
SUMMARY OF THE DISCLOSURE

[0005] Various non-limiting examples of the disclosure are described below.

[0005a] In one aspect, the present disclosure provides a use of an ileal bile acid transporter (IBAT) inhibitor in the manufacture of a medicament for treating cholestatic liver disease in a subject, wherein the treatment is sufficient to result in event-free survival (EFS) of the subject for at least 4 years following the first dose of the IBAT inhibitor, and wherein the treatment increases EFS of the subject by reducing one or more of:

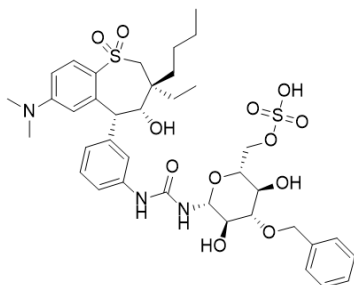
- a) total bilirubin (TB) to 6.5 mg/dL or below;
- b) total serum bile acids (sBA) to 200 μ mol/L or below, and
- c) pruritus score as measured by an Itch Reported Outcome (ItchRO) severity assessment tool by at least 1 point,

wherein the TB, the sBA, or the pruritus score is reduced as compared to the time of first administration of the IBAT inhibitor,



wherein the IBAT inhibitor is

(maralixibat) or a pharmaceutically



acceptable salt thereof, or

(volixibat), or a pharmaceutically

acceptable salt thereof, and wherein the EFS comprises survival in the absence of hepatic decompensation or surgical biliary diversion.

[0006] In one example, the present disclosure provides a method of treating cholestatic liver disease in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of an ileal bile acid transporter (IBAT) inhibitor, wherein the treatment increases event-free survival (EFS) of the subject by reducing one or more of:

a) total bilirubin (TB);

b) total serum bile acids (sBA), and

c) pruritus score as measured by an Itch Reported Outcome (ItchRO) severity assessment tool.

[0007] In one example, the TB is reduced to about 6.5 mg/dL or below.

[0008] In one example, the sBA level is reduced to about 200 μ mol/L or below.

[0009] In one example, the pruritus ItchRO score is reduced by at least about 1 point as compared to the time of first administration of the IBAT inhibitor.

[0010] In one example, the TB, the sBA, or the pruritus score is determined 18 weeks after initiation of the IBAT inhibitor treatment. In one example, the TB, the sBA, or the pruritus score is determined 24 weeks after initiation of the IBAT inhibitor treatment. In one example, the TB, the sBA, or the pruritus score is determined 48 weeks after initiation of the IBAT inhibitor treatment.

[0011] In one example, the TB, the sBA, or the pruritus score is reduced as compared to the time of first administration of the IBAT inhibitor.

administration is sufficient to result in event-free survival of the subject for 6 years following the first dose of the IBAT inhibitor.

[0024] In one example, the cholestatic liver disease is a pediatric cholestatic liver disease.

[0025] In one example, the cholestatic liver disease is an adult cholestatic liver disease.

[0026] In one example, 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 (ALGS), 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.

[0027] In one example, the cholestatic liver disease is ALGS, PFIC, BRIC, PSC, PBC, or biliary atresia.

[0028] In one example, the sBA comprise one or more of TCA, TUDCA, TCDCA, TDCA, TLCA, GCA, GUDCA, GCDCA, GDCA, GLCA, CA, UDCA, CDCA, DCA, and LCA.

[0029] In another example, the present disclosure provides a method of treating cholestatic liver disease with pruritus in a subject in need thereof, the method comprising

[0031] In one example, the pruritus score is determined 18 weeks after initiation of the IBAT inhibitor treatment. In one example, the pruritus score is determined 24 weeks after initiation of the IBAT inhibitor treatment. In one example, the pruritus score is determined 48 weeks after initiation of the IBAT inhibitor treatment.

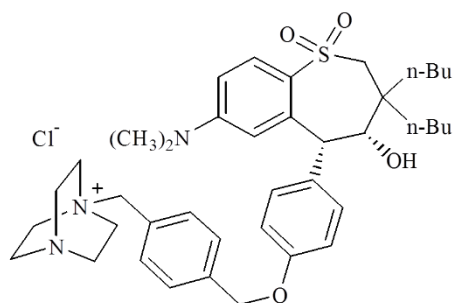
[0032] In another example, the present disclosure provides a method of treating cholestatic liver disease with elevated total serum bile acids (sBA) in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of an IBAT inhibitor or a pharmaceutically acceptable salt thereof, wherein the administration increases event-free survival (EFS) of the subject for at least 18 months following the first dose of the IBAT inhibitor by reducing sBA to about 200 $\mu\text{mol/L}$ or below.

[0033] In one example, the cholestatic liver disease with elevated sBA is selected from the group consisting of ALGS, PFIC, BRIC, PSC, PBC, and biliary atresia.

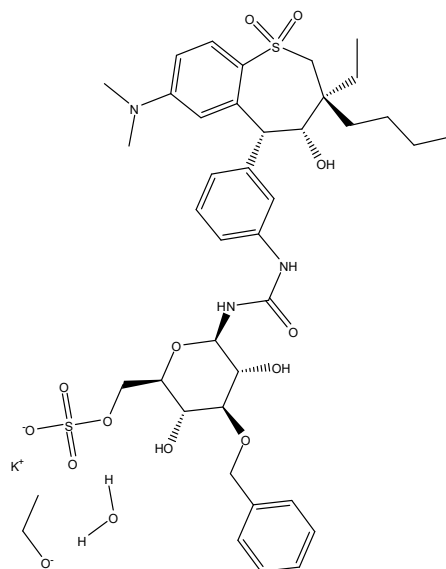
[0034] In one example, the sBA is determined 18 weeks after initiation of the IBAT inhibitor treatment. In one example, the sBA is determined 24 weeks after initiation of the IBAT inhibitor treatment. In one example, the sBA is determined 48 weeks after initiation of the IBAT inhibitor treatment.

[0035] In one example, the sBA comprise one or more of TCA, TUDCA, TCDCA, TDCA, TLCA, GCA, GUDCA, GCDCA, GDCA, GLCA, CA, UDCA, CDCA, DCA, and LCA.

[0036] In another example, the present disclosure provides a method of treating cholestatic liver disease with elevated total bilirubin (TB) in a subject in need thereof,



(maralixibat chloride).



[0048] In one example, the IBAT inhibitor is (potassium).

(volixibat

[0049] In one example, the subject is a pediatric subject. In one example, the pediatric subject is 0 to 18 years of age.

[0050] In one example, the IBAT inhibitor is administered orally.

[0051] In one example, less than 10% of the IBAT inhibitor is systemically absorbed. In one example, less than 30% of the IBAT inhibitor is systemically absorbed.

[0052] In yet another example, the present disclosure provides a method of treating Alagille syndrome in a pediatric subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of maralixibat or a pharmaceutically acceptable salt thereof, wherein the administration increases event-free survival (EFS) of the subject for at least 18 months following the first dose of maralixibat by reducing one or more of:

- a) total bilirubin (TB) to about 6.5 mg/dL or below;
- b) total serum bile acids (sBA) to about 200 μ mol/L or below, and

c) pruritus score as measured by an Itch Reported Outcome (ItchRO) severity assessment tool by at least about 1 point.

[0053] In one example, the treatment increases liver transplant-free survival (TFS) for at least 18 months following the first dose of maralixibat.

[0055] In one example, the maralixibat is maralixibat chloride.

[0056] In one example, the sBA comprise one or more of TCA, TUDCA, TCDCA, TDCA, TLCA, GCA, GUDCA, GCDCA, GDCA, GLCA, CA, UDCA, CDCA, DCA, and LCA.

[0057] These and other examples of the present disclosure will become apparent to those skilled in the art after a reading of the following detailed description of the disclosure, including the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0058] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0059] **Figure 1** shows a Kaplan-Meier Plot for Event-Free Survival in Maralixibat Cohort versus GALA Control Group.

[0060] **Figures 2A-2D** shows Kaplan-Meier plots of EFS according to the following variables: (Fig. 2A) week 48 total bilirubin, (Fig. 2B) week 48 sBA, (Fig. 2C) change from baseline to week 48 ItchRO(Obs), and (Fig. 2D) age at initiation of maralixibat. Data values under each panel indicate the number of patients at each time point. EFS, event-free survival; ItchRO(Obs), itch-reported outcome (observer); pt, point; sBA, serum bile acid.

[0061] **Figures 3A-3C** depict HRQoL scores at baseline and week 48 according to ItchRO response status. PedsQL Generic Core Total Scale Score is shown in Figure 3A, Family Impact

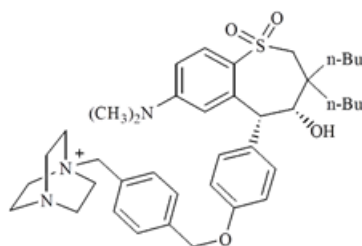
Claims

WHAT IS CLAIMED IS:

1. Use of an ileal bile acid transporter (IBAT) inhibitor in the manufacture of a medicament for treating cholestatic liver disease in a subject, wherein the treatment is sufficient to result in event-free survival (EFS) of the subject for at least 4 years following the first dose of the IBAT inhibitor, and wherein the treatment increases EFS of the subject by reducing one or more of:

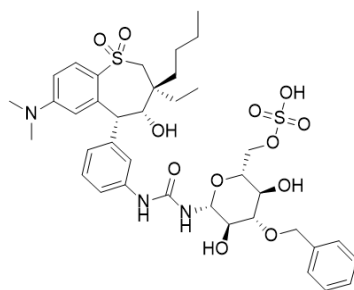
- a) total bilirubin (TB) to 6.5 mg/dL or below;
- b) total serum bile acids (sBA) to 200 μ mol/L or below, and
- c) pruritus score as measured by an Itch Reported Outcome (ItchRO) severity assessment tool by at least 1 point,

wherein the TB, the sBA, or the pruritus score is reduced as compared to the time of first administration of the IBAT inhibitor,



wherein the IBAT inhibitor is

(maralixibat) or a pharmaceutically



acceptable salt thereof, or

(volixibat), or a pharmaceutically

acceptable salt thereof, and wherein the EFS comprises survival in the absence of hepatic decompensation or surgical biliary diversion.

2. The use of claim 1, wherein the TB, the sBA, or the pruritus score is determined 18 weeks after initiation of the IBAT inhibitor treatment.

3. The use of any one of claims 1-2, wherein the TB, the sBA, or the pruritus score is determined 24 weeks after initiation of the IBAT inhibitor treatment.
4. The use of any one of claims 1-3, wherein the TB, the sBA, or the pruritus score is determined 48 weeks after initiation of the IBAT inhibitor treatment.
5. The use of any one of claims 1-4, wherein the EFS comprises survival in the absence of one or more of liver transplantation or death.
6. The use of claim 5, wherein the EFS comprises survival of the subject in the absence of liver transplant.
7. The use of claim 1, wherein treatment with the IBAT inhibitor further results in reduction of cholestatic pruritus.
8. The use of claim 1, wherein the administration is sufficient to result in event-free survival of the subject for at least 18 months following the first dose of the IBAT inhibitor.
9. The use of claim 1 or 8, wherein the administration is sufficient to result in event-free survival of the subject for at least 2 years following the first dose of the IBAT inhibitor.
10. The use of any one of claims 1 and 8-9, wherein the administration is sufficient to result in event-free survival of the subject for 6 years following the first dose of the IBAT inhibitor.
11. The use of any one of claims 1-10, wherein the cholestatic liver disease is a pediatric cholestatic liver disease.
12. The use of any one of claims 1-10, wherein the cholestatic liver disease is an adult cholestatic liver disease.
13. The use of any one of claims 1-12, wherein 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 (ALGS), 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.

14. The use of any one of claims 11-13, wherein the cholestatic liver disease is ALGS, PFIC, BRIC, PSC, PBC, or biliary atresia.

15. The use of any one of claims 1-14, wherein sBA comprise one or more of TCA, TUDCA, TCDCA, TDCA, TLCA, GCA, GUDCA, GCDCA, GDCA, GLCA, CA, UDCA, CDCA, DCA, and LCA.

16. The use of any one of claims 1-15, wherein the IBAT inhibitor is to be administered once daily.

17. The use of any one of claims 1-15, wherein the IBAT inhibitor is to be administered twice daily.

18. The use of any one of claims 1-17, wherein the IBAT inhibitor is to be administered in an amount of 0.1 mg to 100 mg per dose.

19. The use of claim 18, wherein the IBAT inhibitor is to be administered in an amount of 10 mg to 100 mg per dose.

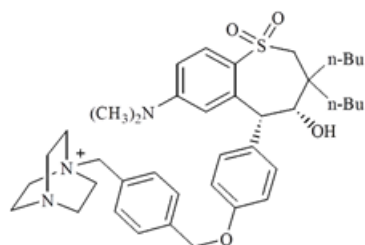
20. The use of any one of claims 1-19, wherein the IBAT inhibitor is to be administered in an amount of 20 mg to 80 mg per dose.

21. The use of any one of claims 1-20, wherein the IBAT inhibitor is to be administered in an amount of 100 ug/kg/day to 1400 ug/kg/day.

22. The use of claim 21, wherein the IBAT inhibitor is to be administered in an amount of 400 ug/kg/day to 800 ug/kg/day.

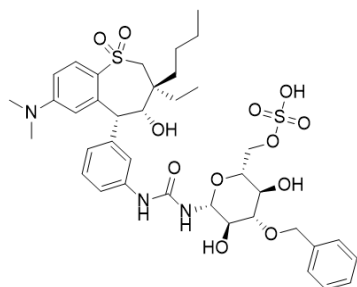
23. The use of any one of claims 1-22, wherein the subject has a BSEP deficiency.

24. The use of any one of claims 1-22, wherein the IBAT inhibitor is



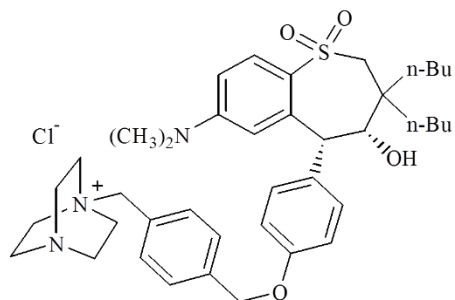
(maralixibat), or a pharmaceutically acceptable salt thereof.

25. The use of any one of claims 1-22, wherein the IBAT inhibitor is

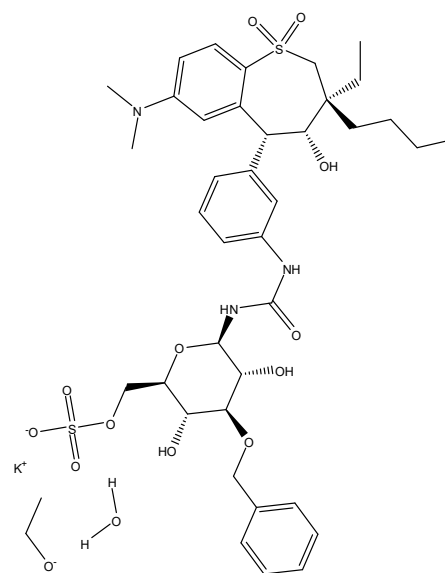


(volixibat), or a pharmaceutically acceptable salt thereof.

26. The use of claim 24, wherein the IBAT inhibitor is



(maralixibat chloride).



27. The use of claim 24, wherein the IBAT inhibitor is (volixibat potassium).
28. The use of any of claims 1-27, wherein the subject is a pediatric subject.
29. The use of claim 28, wherein the pediatric subject is 0 to 18 years of age.
30. The use of any of claims 1-29, wherein the IBAT inhibitor is to be administered orally.
31. The use of any of claims 1-30, wherein less than 10% of the IBAT inhibitor is systemically absorbed.
32. The use of any of claims 1-30, wherein less than 30% of the IBAT inhibitor is systemically absorbed.