

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 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.

[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 $\mu\text{mol/L}$ 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.

[0012] In another aspect, the present disclosure provides a method for providing a prediction of response to an IBAT inhibitor therapy for treatment of cholestatic liver disease in a subject in need thereof by predicting event-free survival (EFS), the method comprising obtaining one or more of total bilirubin (TB) data, total serum bile acids (sBA) data, pruritus reduction data and age of the subject at initiation of treatment with the IBAT inhibitor, and using the data obtained for the subject to predict EFS.

- [0013]** In one example, the EFS is predicted when the TB is less than about 6.5 mg/dL.
- [0014]** In one example, the TB is determined 48 weeks after initiation of the IBAT inhibitor treatment.
- [0015]** In one example, the EFS is predicted when the sBA level after treatment with the IBAT inhibitor is less than about 200 $\mu\text{mol/L}$.
- [0016]** In one example, the sBA level is determined 18 weeks after initiation of the IBAT inhibitor treatment. In one example, the sBA level is determined 24 weeks after initiation of the IBAT inhibitor treatment. In one example, the sBA level is determined 48 weeks after initiation of the IBAT inhibitor treatment.
- [0017]** In one example, the EFS is predicted when the pruritus reduction is at least about 1 point after treatment with the IBAT inhibitor compared to the pruritus at the time of first administration of the IBAT inhibitor, wherein the pruritus is measured by an Itch Reported Outcome (ItchRO) severity assessment tool.
- [0018]** In one example, the pruritus is determined 18 weeks after the initiation of the IBAT inhibitor treatment. In one example, the pruritus is determined 24 weeks after the initiation of the IBAT inhibitor treatment. In one example, the pruritus is determined 48 weeks after the initiation of the IBAT inhibitor treatment.
- [0019]** In one example, the EFS is predicted when the age of the subject at the time of initiation of treatment is equal to or higher than about 36 months.
- [0020]** In one example, the EFS comprises survival in the absence of one or more of hepatic decompensation, surgical biliary diversion, liver transplantation or death.
- [0021]** In one example, the EFS comprises survival of the subject in the absence of liver transplant.
- [0022]** In one example, the treatment with the IBAT inhibitor further results in reduction of cholestatic pruritus.
- [0023]** In one example, 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. In one example, 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. In one example, the

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.

[0028a] In another aspect, the present disclosure provides a use of an IBAT inhibitor or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cholestatic liver disease with pruritus in a subject, wherein the treatment increases event-free survival (EFS) of the subject for at least 18 months following the first dose of the IBAT inhibitor by reducing pruritus score as measured by an Itch Reported Outcome (ItchRO) severity assessment tool by at least about 1 point.

[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

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

[0030] In one example, the cholestatic liver disease with pruritus is selected from the group consisting of ALGS, PFIC, BRIC, PSC, PBC and biliary atresia.

[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.

[0031a] In another aspect, the present disclosure provides a use of an IBAT inhibitor or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cholestatic liver disease with elevated total serum bile acids (sBA) in a subject, wherein the treatment 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.

[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.

[0035a] In another aspect, the present disclosure provides a use of an IBAT inhibitor or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cholestatic liver disease with elevated total bilirubin (TB) in a subject, wherein the treatment increases event-free survival (EFS) of the subject for at least 18 months following the first dose of the IBAT inhibitor by reducing TB to about 6.5 mg/dL or below.

[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,

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 TB to about 6.5 mg/dL or below.

[0037] In one example, the cholestatic liver disease with elevated TB is biliary atresia (BA).

[0038] In one example, the TB is determined 48 weeks after initiation of the IBAT inhibitor treatment.

[0039] In one example, 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. In one example,

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

[0040] In one example, the IBAT inhibitor is administered once daily.

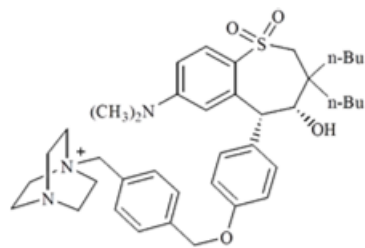
[0041] In one example, the IBAT inhibitor is administered twice daily.

[0042] In one example, the IBAT inhibitor is administered in an amount of about 0.1 mg to about 100 mg per dose. In one example, the IBAT inhibitor is administered in an amount of about 10 mg to about 100 mg per dose. In one example, the IBAT inhibitor is administered in an amount of about 20 mg to about 80 mg per dose.

[0043] In one example, the IBAT inhibitor is administered in an amount of about 100 ug/kg/day to 1400 ug/kg/day. In one example, the IBAT inhibitor is administered in an amount of about 400 ug/kg/day to about 800 ug/kg/day.

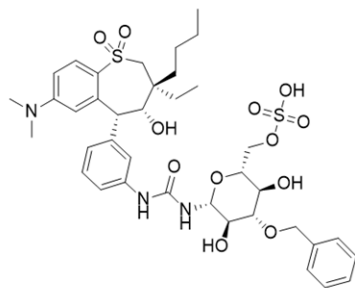
[0044] In one example, the subject has a BSEP deficiency.

[0045] In one example, the IBAT inhibitor is



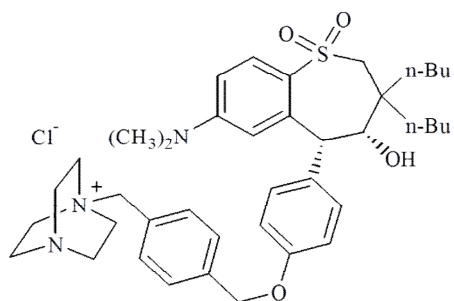
(maralixibat), or a pharmaceutically acceptable salt thereof.

[0046] In one example, the IBAT inhibitor is

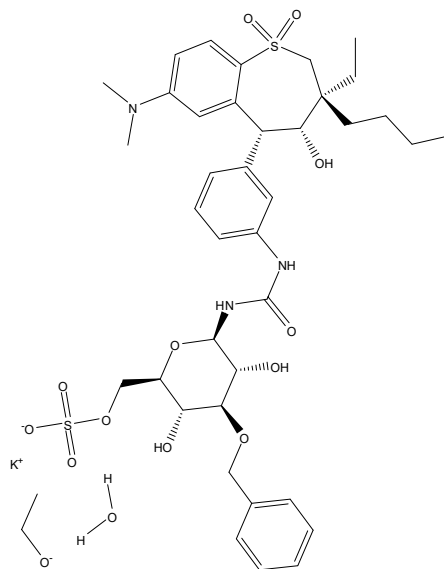


(volixibat), or a pharmaceutically acceptable salt thereof.

[0047] In one example, the IBAT inhibitor is



(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.

[0051a] In another aspect, the present disclosure provides a use of maralixibat or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating Alagille syndrome in a pediatric subject, wherein the treatment 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.

[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.

[0054] In yet another aspect, the present disclosure provides a method for providing a prediction of response to maralixibat therapy for treatment of Alagille syndrome in a subject in need thereof by predicting event-free survival (EFS) for 6 years following the first dose of the maralixibat, the method comprising: obtaining one or more of total bilirubin (TB) data, total serum bile acids (sBA) data, pruritus reduction data and age of the subject at initiation of treatment with maralixibat, and using the data obtained for the subject to predict the EFS.

[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 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.
2. The use of claim 1, wherein the TB is reduced to about 6.5 mg/dL or below.
3. The use of claim 1, wherein the sBA level is reduced to about 200 μ mol/L or below.
4. The use of claim 1, wherein the pruritus ItchRO score is reduced by at least about 1 point as compared to the time of first administration of the IBAT inhibitor.
5. The use of any one of claims 1-4, wherein the TB, the sBA, or the pruritus score is determined 18 weeks after initiation of the IBAT inhibitor treatment.
6. The use of any one of claims 1-5, wherein the TB, the sBA, or the pruritus score is determined 24 weeks after initiation of the IBAT inhibitor treatment.
7. The use of any one of claims 1-6, wherein the TB, the sBA, or the pruritus score is determined 48 weeks after initiation of the IBAT inhibitor treatment.
8. The use of any one of claims 1-7, wherein the TB, the sBA, or the pruritus score is reduced as compared to the time of first administration of the IBAT inhibitor.
9. A method for providing a prediction of response to an IBAT inhibitor therapy for treatment

of cholestatic liver disease in a subject in need thereof by predicting event-free survival (EFS), the method comprising:

obtaining one or more of total bilirubin (TB) data, total serum bile acids (sBA) data, pruritus reduction data and age of the subject at initiation of treatment with the IBAT inhibitor, and using the data obtained for the subject to predict EFS.

10. The method of claim 9, wherein the EFS is predicted when the TB is less than about 6.5 mg/dL.

11. The method of claim 10, wherein the TB is determined 48 weeks after initiation of the IBAT inhibitor treatment.

12. The method of claim 9, wherein the EFS is predicted when the sBA level after treatment with the IBAT inhibitor is less than about 200 $\mu\text{mol/L}$.

13. The method of claim 11, wherein the sBA level is determined 18 weeks after initiation of the IBAT inhibitor treatment.

14. The method of claims 12 or 13, wherein the sBA level is determined 24 weeks after initiation of the IBAT inhibitor treatment.

15. The method of any one of claims 12-14, wherein the sBA level is determined 48 weeks after initiation of the IBAT inhibitor treatment.

16. The method of claim 9, wherein the EFS is predicted when the pruritus reduction is at least about 1 point after treatment with the IBAT inhibitor compared to the pruritus at the time of first administration of the IBAT inhibitor, wherein the pruritus is measured by an Itch Reported Outcome (ItchRO) severity assessment tool.

17. The method of claim 16, wherein the pruritus is determined 18 weeks after the initiation of the IBAT inhibitor treatment.

18. The method of claim 16 or 17, wherein the pruritus is determined 24 weeks after the initiation of the IBAT inhibitor treatment.
19. The method of claim 16-18, wherein the pruritus is determined 48 weeks after the initiation of the IBAT inhibitor treatment.
20. The method of claim 9, wherein the EFS is predicted when the age of the subject at the time of initiation of treatment is equal to or higher than about 36 months.
21. The method of any one of claims 1-21, wherein the EFS comprises survival in the absence of one or more of hepatic decompensation, surgical biliary diversion, liver transplantation or death.
22. The method of claim 21, wherein the EFS comprises survival of the subject in the absence of liver transplant.
23. The use of claim 1, wherein treatment with the IBAT inhibitor further results in reduction of cholestatic pruritus.
24. 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.
25. The use of claim 1 or 24, 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.
26. The use of any one of claims 1 and 24-25, 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.
27. The use or method of any one of claims 1-26, wherein the cholestatic liver disease is a pediatric cholestatic liver disease.

28. The use or method of any one of claims 1-26, wherein the cholestatic liver disease is an adult cholestatic liver disease.

29. The use or method of any one of claims 1-28, 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.

30. The use or method of any one of claims 27-29, wherein the cholestatic liver disease is ALGS, PFIC, BRIC, PSC, PBC, or biliary atresia.

31. The use or method of any one of claims 1-30, wherein sBA comprise one or more of TCA, TUDCA, TCDCA, TDCA, TLCA, GCA, GUDCA, GCDCA, GDCA, GLCA, CA, UDCA, CDCA, DCA, and LCA.

32. Use of an IBAT inhibitor or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cholestatic liver disease with pruritus in a subject, wherein the treatment increases event-free survival (EFS) of the subject for at least 18 months following the first dose of the IBAT inhibitor by reducing pruritus score as measured by an Itch Reported Outcome (ItchRO) severity assessment tool by at least about 1 point.

33. The use of claim 32, wherein the cholestatic liver disease with pruritus is selected from the group consisting of ALGS, PFIC, BRIC, PSC, PBC, and biliary atresia.

34. The use of claim 32 or 33, wherein the pruritus score is determined 18 weeks after initiation of the IBAT inhibitor treatment.
35. The use of any one of claims 32-34, wherein the pruritus score is determined 24 weeks after initiation of the IBAT inhibitor treatment.
36. The use of any one of claims 32-35, wherein the pruritus score is determined 48 weeks after initiation of the IBAT inhibitor treatment.
37. Use of an IBAT inhibitor or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cholestatic liver disease with elevated total serum bile acids (sBA) in a subject, wherein the treatment 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.
38. The use of claim 37, wherein the cholestatic liver disease with elevated sBA is selected from the group consisting of ALGS, PFIC, BRIC, PSC, PBC, and biliary atresia.
39. The use of claim 37 or 38, wherein the sBA is determined 18 weeks after initiation of the IBAT inhibitor treatment.
40. The use of any one of claims 37-39, wherein the sBA is determined 24 weeks after initiation of the IBAT inhibitor treatment.
41. The use of any one of claims 37-40, wherein the sBA is determined 48 weeks after initiation of the IBAT inhibitor treatment.
42. The use of any one of claims 37-41, wherein sBA comprise one or more of TCA, TUDCA, TCDCA, TDCA, TLCA, GCA, GUDCA, GCDCA, GDCA, GLCA, CA, UDCA, CDCA, DCA, and LCA.

43. Use of an IBAT inhibitor or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cholestatic liver disease with elevated total bilirubin (TB) in a subject, wherein the treatment increases event-free survival (EFS) of the subject for at least 18 months following the first dose of the IBAT inhibitor by reducing TB to about 6.5 mg/dL or below.
44. The use of claim 43, wherein the cholestatic liver disease with elevated TB is biliary atresia (BA).
45. The use of claim 43, wherein the TB is determined 48 weeks after initiation of the IBAT inhibitor treatment.
46. The use of any one of claims 32-45, 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.
47. The use of any one of claims 32-46, 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.
48. The use or method of any one of claims 1-47, wherein the IBAT inhibitor is to be administered once daily.
49. The use or method of any one of claims 1-47, wherein the IBAT inhibitor is to be administered twice daily.
50. The use or method of any one of claims 1-49, wherein the IBAT inhibitor is to be administered in an amount of about 0.1 mg to about 100 mg per dose.
51. The use or method of claim 50, wherein the IBAT inhibitor is to be administered in an amount of about 10 mg to about 100 mg per dose.
52. The use or method of any one of claims 1-51, wherein the IBAT inhibitor is to be

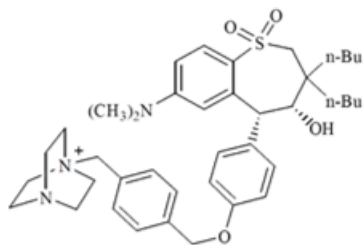
administered in an amount of about 20 mg to about 80 mg per dose.

53. The use or method of any one of claims 1-52, wherein the IBAT inhibitor is to be administered in an amount of about 100 ug/kg/day to 1400 ug/kg/day.

54. The use or method of claim 53, wherein the IBAT inhibitor is to be administered in an amount of about 400 ug/kg/day to about 800 ug/kg/day.

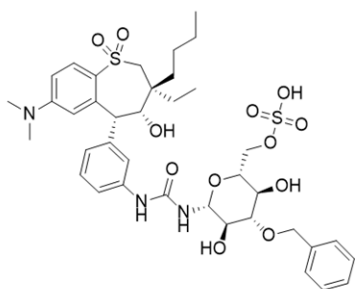
55. The use or method of any one of claims 1-54, wherein the subject has a BSEP deficiency.

56. The use or method of any one of claims 1-54, wherein the IBAT inhibitor is



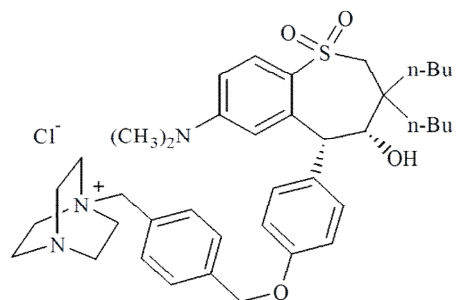
(maralixibat), or a pharmaceutically acceptable salt thereof.

57. The use or method of any one of claims 1-54, wherein the IBAT inhibitor is



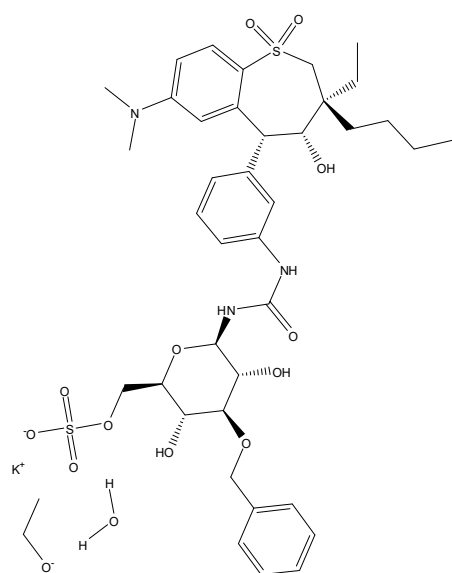
(volixibat), or a pharmaceutically acceptable salt thereof.

58. The use or method of claim 56, wherein the IBAT inhibitor is



(maralixibat chloride).

59. The use or method of claim 56, wherein the IBAT inhibitor is



(volixibat potassium).

60. The use or method of any of claims 1-59, wherein the subject is a pediatric subject.
61. The use or method of claim 60, wherein the pediatric subject is 0 to 18 years of age.
62. The use or method of any of claims 1-61, wherein the IBAT inhibitor is to be administered orally.
63. The use or method of any of claims 1-62, wherein less than 10% of the IBAT inhibitor is systemically absorbed.
64. The use or method of any of claims 1-63, wherein less than 30% of the IBAT inhibitor is

systemically absorbed.

65. Use of maralixibat or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating Alagille syndrome in a pediatric subject, wherein the treatment 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.

66. The use of claim 65, wherein the treatment increases liver transplant-free survival (TFS) for at least 18 months following the first dose of maralixibat.

67. A method for providing a prediction of response to maralixibat therapy for treatment of Alagille syndrome in a subject in need thereof by predicting event-free survival (EFS) for 6 years following the first dose of the maralixibat, the method comprising:

obtaining one or more of total bilirubin (TB) data, total serum bile acids (sBA) data, pruritus reduction data and age of the subject at initiation of treatment with maralixibat, and using the data obtained for the subject to predict the EFS.

68. The use or method of any one of claims 65-67, wherein the maralixibat is maralixibat chloride.

69. The use or method of any one of claims 65-68, wherein sBA comprise one or more of TCA, TUDCA, TCDCA, TDCA, TLCA, GCA, GUDCA, GCDCA, GDCA, GLCA, CA, UDCA, CDCA, DCA, and LCA.