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(54) **Title:** GENOTYPE AND DOSE-DEPENDENT RESPONSE TO AN ASBTI IN PATIENTS WITH BILE SALT EXPORT PUMP DEFICIENCY

(57) **Abstract:** Provided herein are methods for treating or ameliorating cholestatic liver disease in a subject in need thereof. The methods include administering an Apical Sodium-dependent Bile Acid Transport Inhibitor (ASBTI) to the subject. The methods include determining a genotype of the subject and predicting subject response to the ASBTI administration based upon the genotype. The methods further include determining, adjusting, or modulating a dose of the ASBTI administered to the subject based upon the genotype or upon measurements of clinically relevant disease parameters.

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GENOTYPE AND DOSE-DEPENDENT RESPONSE TO AN ASBTI IN PATIENTS WITH BILE SALT EXPORT PUMP DEFICIENCY

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit under 35 U.S.C. §119(e) of U.S. Provisional Applications Nos. 62/504,523, filed February 12, 2019, 62/863,904, filed June 20, 2019, 62/908,431, filed September 30, 2019, and 62/932,015, filed November 7, 2019, which are incorporated herein by reference in their entirety for all purposes.

FIELD OF THE INVENTION

[0002] The present invention relates generally to methods for treating or ameliorating cholestatic liver disease. In particular, the invention relates to methods for modulating a dosage of an Apical Sodium-dependent Bile Acid Transport Inhibitor (ASBTI) administered to a subject and to methods for using subject genotype to predict response to ASBTI administration at a particular dosage level.

BACKGROUND

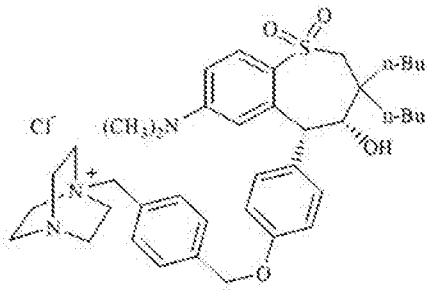
[0003] Hypercholemia and cholestatic liver diseases are liver diseases associated with impaired bile secretion (i.e., cholestasis), associated with and often secondary to the intracellular accumulation of bile acids/salts in the hepatocyte. Hypercholemia is characterized by increased serum concentration 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 (PFIC) types 1, 2, and 3, which are diseases that affect children.

[0004] Neonatal respiratory distress syndrome and lung pneumonia is often associated with intrahepatic cholestasis of pregnancy. Active treatment and prevention are 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.

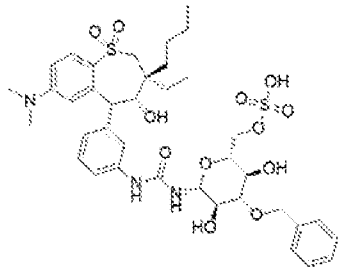
SUMMARY OF THE INVENTION

[0005] Various non-limiting aspects and embodiments of the invention are described below.

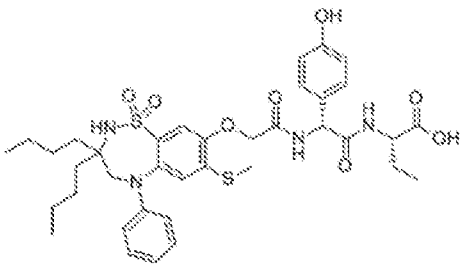
[0006] In one aspect, the present invention provides a method for treating or ameliorating cholestatic liver disease in a subject in need thereof, wherein the subject has a bile salt export pump (BSEP) deficiency and the method comprises administering to the subject an Apical Sodium-dependent Bile Acid Transport Inhibitor (ASBTI). In certain embodiments, the ASBTI is



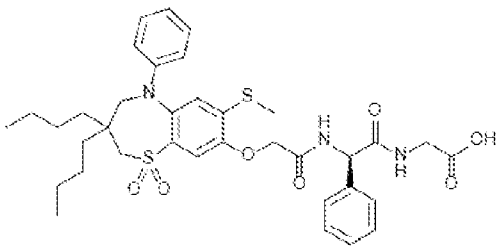
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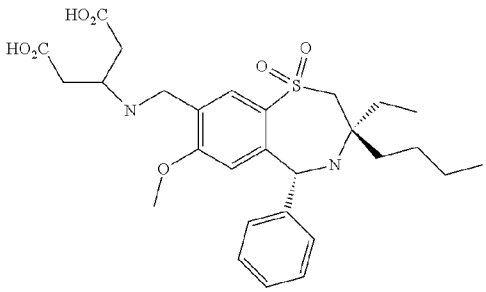
(volixibat),



(odevixibat),



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(GSK2330672), or a pharmaceutically acceptable salt thereof. In certain embodiments, the ASBTI is maralixibat, or a pharmaceutically acceptable salt thereof. In some embodiments, the ASBTI is volixibat, or a pharmaceutically acceptable salt thereof. In various embodiments, the ASBTI is odevixibat, or a pharmaceutically acceptable salt thereof. In some embodiments, the ASBTI is elobixibat, or a pharmaceutically acceptable salt thereof. In some embodiments, the ASBTI is GSK2330672, or a pharmaceutically acceptable salt thereof.

[0007] In various embodiments, the cholestatic liver disease is progressive familial intrahepatic cholestasis type 2 (PFIC 2), benign recurrent intrahepatic cholestasis (BRIC) or intrahepatic cholestasis of pregnancy (ICP), or biliary atresia. In some embodiments, the subject has residual BSEP function. In various embodiments, the BSEP deficiency results in impaired or reduced bile flow or cholestasis.

[0008] In some embodiments, an *ABCB11* gene of the subject comprises a non-truncating mutation. In various embodiments, the *ABCB11* gene comprises one or more of E297G, D482G, an alternative missense mutation, or a combination thereof. In certain embodiments, the *ABCB11* gene comprises an E297G or a D482G mutation, or both. In various embodiments, the *ABCB11* gene comprises a missense mutation and not an E297G or D482G mutation.

[0009] In some embodiments, the method further comprises determining a genotype of the subject. In some embodiments, determining the genotype comprises identifying and characterizing a mutation in the *ABCB11* gene. In certain embodiments, the *ABCB11* gene of the subject is characterized as comprising only non-truncating mutations.

[0010] In various embodiments, the method comprises determining a ratio of serum 7α-hydroxy-4-cholesten-2-one (7αC4) concentration to serum bile acid (sBA) concentration (7αC4:sBA) prior to administering the ASBTI at a first dose level (baseline ratio), and further determining 7αC4:sBA after the ASBTI administration, where the ASBTI administration results in a 7αC4:sBA ratio about 2-fold or greater higher than the baseline 7αC4:sBA ratio. In certain embodiments, if the 7αC4:sBA ratio begins to decrease or decreases to less than 2-

fold or greater higher than baseline, a second dose level of the ASBTI is administered to the subject. The second dose level is higher than the first dose level.

[0011] In various embodiments, the method comprises determining a ratio of serum 7αC4 concentration to sBA concentration (7αC4:sBA) prior to administering the ASBTI at a first dose level (baseline ratio), and further determining 7αC4:sBA after the ASBTI administration, wherein if the ASBTI administration fails to result in a 7αC4:sBA ratio about 2-fold or greater higher than the baseline 7αC4:sBA ratio, the subject is administered a second dose level of the ASBTI, wherein the second dose level is higher than the first dose level.

[0012] In various embodiments, the method further comprises modulating a dose of the ASBTI, the modulating comprising determining a ratio of serum 7αC4 concentration to sBA concentration (7αC4:sBA) prior to administering the ASBTI at a first dose level (baseline ratio), and further determining 7αC4:sBA after the ASBTI administration, wherein if the ASBTI administration fails to result in a 7αC4:sBA ratio about 2-fold or greater higher than the baseline 7αC4:sBA ratio the ASBTI is then administered at a second dose level that does result in a 7αC4:sBA ratio that is about a 2-fold or greater higher than the baseline ratio. In various embodiments, the second dose is at least about twice and less than about five times the first dose.

[0013] In various embodiments, the method further comprises modulating a dose of the ASBTI, the modulating comprising determining a ratio of serum 7αC4 concentration to sBA concentration (7αC4:sBA) prior to administering the ASBTI at a first dose level (baseline ratio), and further determining 7αC4:sBA after the ASBTI administration, wherein if a treating physician believes the ratio could be elevated beyond the current level with a higher dose level of the ASBTI, then the subject is administered the ASBTI at a second dose level that results in a 7αC4:sBA ratio that is higher than the baseline ratio.

[0014] In certain embodiments, the subject is a pediatric subject under 18 years of age. In some embodiments, administration of the ASBTI results in improved growth of the subject relative to baseline growth. In various embodiments, the improved growth of the subject is measured as an increase in height z-score.

[0015] In some embodiments, the ASBTI is administered at a daily dose of from about 140 μg/kg to about 1400 μg/kg. In some embodiments, the ASBTI is administered once daily. In various embodiments, the ASBTI is administered twice daily. In various embodiments, the ASBTI is administered at a daily dose of from about 5 mg/day to about 100 mg/day. In some

embodiments, the ASBTI is administered regularly for a period of at least one year. In certain embodiments, the ASBTI is administered regularly for a period of at least 4 years.

[0016] In various embodiments, the administration of the ASBTI results in a reduction in a symptom or a change in a disease-relevant laboratory measure of the cholestatic liver disease that is maintained for at least one year. In various embodiments, the reduction in a symptom or a change in a disease-relevant laboratory measure comprises a reduction in sBA concentration, an increase in serum 7αC4 concentration, an increase in a ratio of serum 7αC4 concentration to sBA concentration (7αC4:sBA), a reduction in pruritis, an increase in a quality of life inventory score, an increase in a quality of life inventory score related to fatigue, or a combination thereof. In some embodiments, the reduction in the symptom or a change in a disease-relevant laboratory measure is determined relative to a baseline level. In various embodiments, the subject is a pediatric subject under 18 years of age, and the reduction in a symptom or a change in a disease-relevant laboratory measure comprises an increase in growth.

[0017] In some embodiments, the administration of the ASBTI results in an increase in serum 7αC4 concentration. In various embodiments, the serum 7αC4 concentration is increased from about 1.5-fold to about 40-fold relative to baseline. In some embodiments, the administration of the ASBTI results in an increase in a ratio of serum 7αC4 concentration to sBA concentration (7αC4:sBA). In certain embodiments, the 7αC4:sBA is increased by from about 2-fold to about 5,000-fold relative to baseline.

[0018] In various embodiments, the administration of the ASBTI results in an increase in fecal bile acids (fBA) of at least 100% relative to baseline. In some embodiments, the administration of the ASBTI results in a decrease in sBA concentration of at least about 70% relative to baseline.

[0019] In various embodiments, the administration of the ASBTI results in a reduction in severity of pruritus. In some embodiments, the reduction in severity of pruritis is measured as a reduction of at least 1.0 in an observer-reported itch reported outcome (ITCHRO(OBS)) score. In some embodiments, the administration of the ASBTI results in an ITCHRO(OBS) score of ≤1. In various embodiments, the administration of the ASBTI results in an increase in a quality of life inventory score.

[0020] In some embodiments, the quality of life inventory score is a health-related quality of life (HRQoL) score. In some embodiments, the quality of life inventory score is a Pediatric

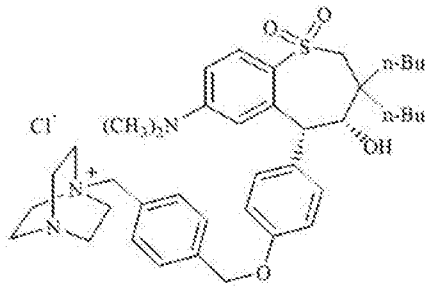
Quality of Life Inventory (PedsQL) score, and the PedsQL score is increased by at least 10% relative to baseline.

[0021] In various embodiments, the serum bilirubin concentration is at pre-administration baseline level at about 4 months after first administration of the ASBTI. In various embodiments, serum alanine aminotransferase (ALT) concentration is at pre-administration baseline level at about 4 months after first administration of the ASBTI. In some embodiments, serum aspartate aminotransferase (AST) concentration, and serum bilirubin concentration are within a normal range at about 4 months after first administration of the ASBTI. In some embodiments, the administration of the ASBTI results in serum ALT concentration decreasing by at least about 10% relative to baseline.

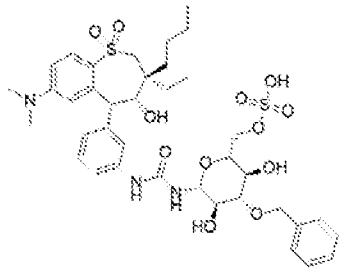
[0022] In various embodiments, the subject has biliary atresia or intrahepatic cholestasis of pregnancy.

[0023] In one aspect, the present invention provides a method for predicting subject response to treatment of a cholestatic liver disease. The treatment comprises administering to the subject in need of such treatment an ASBTI. The method comprises determining a genotype of the subject and predicting subject response to the treatment based upon the genotype.

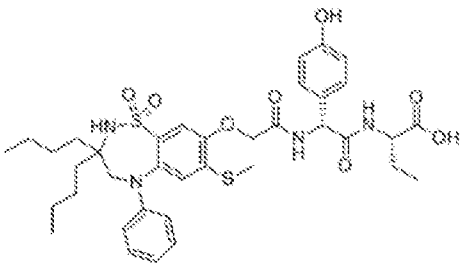
[0024] In various embodiments, the ASBTI is



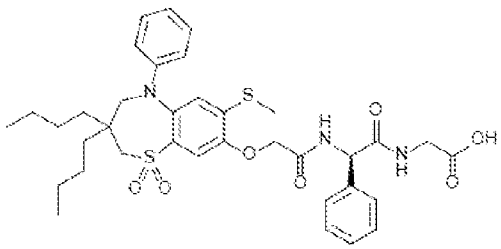
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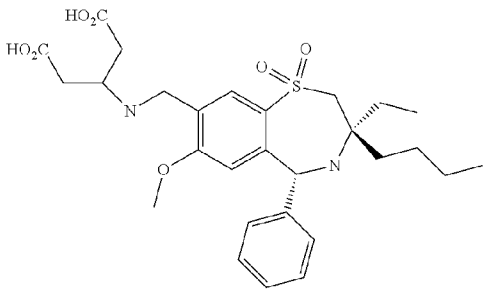
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(GSK2330672), or a pharmaceutically acceptable salt thereof. In some embodiments, the ASBTI is maralixibat, or an alternative pharmaceutically acceptable salt thereof. In certain embodiments, the ASBTI is volixibat, or a pharmaceutically acceptable salt thereof. In various embodiments, the ASBTI is odevixibat, or a pharmaceutically acceptable salt thereof. In some embodiments, the ASBTI is elobixibat, or a pharmaceutically acceptable salt thereof. In various embodiments, the ASBTI is GSK2330672, or a pharmaceutically acceptable salt thereof.

[0025] In various embodiments, the method includes determining the genotype comprises determining a sequence of an *ABCB11* gene. In some embodiments, the method includes

identifying and characterizing a mutation of the *ABCB11* gene. In various embodiments, the method further comprises predicting that the subject will not be responsive to administration of the ASBTI if the *ABCB11* gene comprises a truncating mutation. In some embodiments, the method comprises predicting that the subject will not be responsive to administration of the ASBTI if the *ABCB11* gene comprises a mutation resulting in total loss of BSEP activity. In some embodiments, the method includes predicting that the subject will be responsive to administration of the ASBTI if the *ABCB11* gene comprises mutations that result in residual BSEP activity and the *ABCB11* gene comprises no mutations that result in absence of BSEP activity. In some embodiments, the *ABCB11* gene comprises one or more of an E297G, D482G, an alternative missense mutation, or some combination thereof. In various embodiments, the method includes administering an ASBTI to the subject if the subject is predicted to be responsive to the administration of the ASBTI.

[0026] In some embodiments, the subject has biliary atresia or intrahepatic cholestasis of pregnancy.

[0027] In one aspect, the present invention provides a method for treating or ameliorating cholestatic liver disease in a subject in need thereof. The subject has a BSEP deficiency. The method includes determining a genotype of the subject, using the genotype of the subject to predict whether the subject will be or will not be responsive to treatment with an ASBTI, and administering an ASBTI to the subject if the subject is predicted to be responsive to administration of the ASBTI.

[0028] In various embodiments, determining the genotype comprises determining a sequence of an *ABCB11* gene. In some embodiments, the method includes identifying and characterizing a mutation of the *ABCB11* gene. In various embodiments, the method comprises predicting that the subject will not be responsive to administration of the ASBTI if the *ABCB11* gene comprises a truncating mutation. In some embodiments, the method includes predicting that the subject will not be responsive to administration of the ASBTI if the *ABCB11* gene comprises a mutation resulting in total loss of BSEP activity. In some embodiments, the method includes predicting that the subject will be responsive to administration of the ASBTI if the *ABCB11* gene comprises mutations that result in residual BSEP activity and the *ABCB11* gene comprises no mutations that result in absence of BSEP activity. In various embodiments, the *ABCB11* gene comprises one or more of an E297G, D482G, an alternative missense mutation, or some combination thereof.

[0029] In various embodiments, the method includes determining a ratio of serum 7αC4 concentration to serum bile acid (sBA) concentration (7αC4:sBA) prior to administering the ASBTI at a first dose (baseline ratio), and further determining the 7αC4:sBA after the ASBTI administration. In some embodiments, the method includes administering a second dose of the ASBTI, where the second dose is greater than the first dose, if after the administration of the first dose of the ASBTI the 7αC4:sBA is not maintained about >2-fold higher than the baseline ratio.

[0030] In certain embodiments, the method comprises administering a second dose of the ASBTI, where the second dose is greater than the first dose, if the 7αC4:sBA initially increases by at least >2-fold higher than the baseline ratio and then begins to decrease back to the baseline ratio. In some embodiments, the second dose is at least about twice and less than about five times the second dose.

[0031] In some embodiments, the subject is a pediatric subject under 18 years of age. In various embodiments, the administration of the ASBTI results in improved growth of the subject. In various embodiments, improved growth of the subject is measured as an increase in height z-score.

[0032] In some embodiments, the ASBTI is administered at a daily dose of from about 140 µg/kg to about 1400 µg/kg. In various embodiments ,the ASBTI is administered once daily. In some embodiments, the ASBTI is administered twice daily. In certain embodiments, the ASBTI is administered at a dose of from about 5 mg/day to about 100 mg/day. In various embodiments, the ASBTI is administered regularly for a period of at least one year. In some embodiments, the ASBTI is administered regularly for a period of at least 4 years.

[0033] In various embodiments, administration of the ASBTI results in a reduction in a symptom or a change in a disease-relevant laboratory measure of the cholestatic liver disease that is maintained for at least one year. In various embodiments, the reduction in a symptom or a change in a disease-relevant laboratory measure comprises a reduction in sBA concentration, an increase in serum 7αC4 concentration, an increase in a ratio of serum 7αC4 concentration to sBA concentration (7αC4:sBA), a reduction in pruritis, an increase in a quality of life inventory score, an increase in a quality of life inventory score related to fatigue, or a combination thereof. In some embodiments, the reduction in the symptom or a change in a disease-relevant laboratory measure is determined relative to a baseline level. In various embodiments, the subject is a pediatric subject under 18 years of age and the

reduction in a symptom or a change in a disease-relevant laboratory measure comprises an increase in growth.

[0034] In certain embodiments, the administration of the ASBTI results in an increase in serum 7αC4 concentration. In various embodiments, the serum 7αC4 concentration is increased from about 1.5-fold to about 40-fold relative to baseline. In some embodiments, the serum 7αC4 concentration is increased by at least 100% relative to baseline.

[0035] In some embodiments, the administration of the ASBTI results in an increase in a ratio of serum 7αC4 concentration to sBA concentration (7αC4:sBA). In some embodiments, 7αC4:sBA is increased by from about 2-fold to about 5,000-fold relative to baseline.

[0036] In various embodiments, the administration of the ASBTI results in an increase in fBA of at least 100% relative to baseline. In some embodiments, the administration of the ASBTI results in a decrease in sBA concentration of at least about 70% relative to baseline.

[0037] In some embodiments, administration of the ASBTI results in a reduction in severity of pruritus. In various embodiments, the reduction in severity of pruritis is measured as a reduction of at least 1.0 in an observer-reported itch reported outcome (ITCHRO(OBS)) score relative to baseline. In some embodiments, the administration of the ASBTI results in an ITCHRO(OBS) score of ≤1.

[0038] In various embodiments, the administration of the ASBTI results in an increase in a quality of life inventory score. In some embodiments, the quality of life inventory score is a health-related quality of life (HRQoL) score. In various embodiments, the quality of life inventory score is a Pediatric Quality of Life Inventory (PedsQL) score. In certain embodiments, the PedsQL score is increased by at least 10% relative to baseline.

[0039] In some embodiments, serum bilirubin concentration is at pre-administration baseline level at about 4 months after first administration of the ASBTI. In various embodiments, serum ALT concentration is at pre-administration baseline level at about 4 months after first administration of the ASBTI. In various embodiments, serum ALT concentration, serum AST concentration, and serum bilirubin concentration being are within a normal range at about 4 months after first administration of the ASBTI. In certain embodiments, the administration of the ASBTI results in serum ALT concentration decreasing by at least about 10% relative to baseline.

[0040] In various embodiments, the subject has biliary atresia or intrahepatic cholestasis of pregnancy. In some embodiments, the subject has PFIC 2.

[0041] These and other aspects of the present invention will become apparent to those skilled in the art after a reading of the following detailed description of the invention, including the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0042] **Figure 1** provides a schematic diagram summarizing physiological effects of maralixibat administration in a patient. CYP7A1, cholesterol 7α-hydroxylase; FGF, fibroblast growth factor; FXR, farnesoid X receptor.

[0043] **Figure 2** shows a schematic providing an overview of a dosing regimen used in an INDIGO phase 2 open-label safety and efficacy clinical study (INDIGO clinical study) of maralixibat in children with PFIC. The clinical study investigated long-term exposure to maralixibat.

[0044] **Figures 3A-3F** each provide quantitative summaries of response indicators measured for six responders that participated in the INDIGO clinical study. The six responders were a girl aged 3 years (**Fig. 3A**), a boy aged 10 years (**Fig. 3B**), a girl aged 6 years and sister of the boy aged 10 years (**Fig. 3C**), a girl aged 4 years (**Fig. 3D**), a boy aged 3 years (**Fig. 3E**), and a girl aged 1 year (**Fig. 3F**). Each of **Figs. 3A-3F** provides three scatter plots plotting sBA levels (concentrations), pruritus severity score, and PEDIATRIC QUALITY OF LIFE INVENTORY (PEDSQL) scores against study week, respectively. Pruritus severity score was measured according to the clinical scratch score (CSS) and Itch Reported Outcome (ITCHRO) score. Each of **Figs. 3A-3F** also provides a summary of changes observed in ALT (alanine aminotransferase) and AST (aspartate aminotransferase) levels, bilirubin levels, and C4 levels for each responder.

[0045] **Figure 4** depicts a scatter plot showing height Z-score change from baseline over time for responders and non-responders in the INDIGO clinical study. The decrease in average height Z-score at week 60 is due to one patient not having a measurement for that time point.

[0046] **Figures 5A and 5B** provide scatter plots plotting serum bile acids (sBA) concentration over time for patients that participated in the INDIGO clinical study. **Fig. 5A** plots sBA concentrations over time for patients having non-truncating bile salt export pump (BSEP, which is encoded by the *ABCB11* gene) mutations. **Fig. 5B** plots sBA concentrations over time for patients having truncating BSEP mutations. **Figs. 5A-5B** demonstrate that sBA responses differed by BSEP mutation status. Black filled circles indicate termination. White

filled circles indicate start of BID dosing (280 μg/kg BID). In **Figs. 5A** and **5B** lines corresponding to non-responders are marked with a star.

[0047] **Figure 6** provides a scatter plot plotting observer-reported itch reported outcome (ITCHRO(OBS)) weekly average scores for patients participating in the INDIGO clinical study and having non-truncating BSEP mutations. **Fig. 6** demonstrates that ITCHRO(OBS) response was sustained over years and that >50% (10/19) patients demonstrated a ≥1.0 pt. reduction in ITCHRO(OBS) score. Black filled circles indicate termination. White filled circles indicate commencement of BID dosing (280 μg/kg BID). The ITCHRO(OBS) scale range is 0 to 4. In **Fig. 6** lines corresponding to non-responders are marked with a star.

[0048] **Figure 7** provides a scatter plot plotting mean serum 7α-hydroxy-4-choesten-3-one (7αC4 or C4) concentration over time for patients participating in the INDIGO clinical study and having non-truncating BSEP mutations. **Fig. 7** demonstrates that non-truncating BSEP mutation responders showed significant increases in 7αC4 concentration. Black filled circles indicate termination. White filled circles indicate commencement of BID dosing (280 μg/kg BID). The ITCHRO(OBS) scale range is 0 to 4. In **Fig. 7** lines corresponding to non-responders are marked with a star.

[0049] **Figure 8** provides a scatter plot showing the ratio of 7αC4 concentration to sBA concentration (7αC4:sBA) over time for patients participating in the INDIGO clinical study and having non-truncating BSEP mutations. **Fig. 8** demonstrates that non-truncating BSEP mutation responders had significantly different 7αC4:sBA ratios than non-responders. Two non-truncating BSEP mutation responders showed an increase in 7αC4:sBA ratio following dose elevation. Black filled circles indicate termination. White filled circles indicate commencement of BID dosing (280 μg/kg BID). The ITCHRO(OBS) scale range is 0 to 4. In **Fig. 8** lines corresponding to non-responders are marked with a star.

[0050] **Figure 9** provides a bar graph showing mean change from baseline to day 6 and 7 in fecal bile acid (fBA) excretion across indicated doses of maralixibat, volixibat, and placebo for a phase 1, blinded, placebo controlled, dose ranging clinical study (NCT02475317). BID, twice daily; QD, once daily; SE, standard error.

[0051] **Figure 10** provides a bar graph showing mean change from baseline to day 7 in serum 7αC4 concentration across indicated doses of maralixibat, volixibat, and placebo. BID, twice daily; fBA, fecal bile acids; QD, once daily; SE, standard error.

[0052] **Figure 11** provides a bar graph showing mean ITCHRO weekly sum scores in an overall population of participants in a 14-week, single-arm, open-label, phase 2a, proof-of-

concept study of maralixibat (CAMEO clinical study) having any pruritus at baseline, and participants with ITCHRO daily scores ≥4 at baseline.

[0053] **Figure 12** shows bar plots of sBA concentration (left panel) and 7αC4 concentration (right panel) in an overall population participating in the CAMEO clinical study and in participants with ITCHRO daily scores ≥4 at baseline.

[0054] **Figure 13** shows bar plots of serum autotaxin concentration (left panel) and serum low-density lipoprotein cholesterol (LDL-C) concentration (right panel) in the overall population participating in the CAMEO clinical study and in participants with ITCHRO daily scores ≥4 at baseline.

[0055] **Figure 14** shows a bar plot of percentage change from baseline to week 14 or early termination on efficacy measures including ITCHRO score (1-10 daily score), sBA concentration, and serum autotaxin concentration in six participants in the CAMEO clinical study with ITCHRO daily scores ≥4 at baseline.

[0056] **Figure 15** provides a diagram summarizing the clinical study design for a double blind, randomized, placebo controlled drug withdrawal study with a long-term open label treatment period of maralixibat 400 μg/kg QD (ICONIC clinical study).

[0057] **Figure 16** provides a diagram summarizing the disposition of participants in the ICONIC clinical study.

[0058] **Figures 17A and 17B** demonstrate significant improvements in sBA levels versus baseline and placebo in participants in the ICONIC clinical study. **Fig. 17A** shows a graph plotting mean change in sBA concentration from baseline in all participants through week 48. **Fig. 17B** shows a bar graph showing mean change in sBA from week 8-22 in sBA responders during a randomized withdrawal.

[0059] **Figure 18** shows a plot of mean sBA concentrations for participants in the ICONIC clinical study during the core study (first 48 weeks) and during the extension (period after 48 weeks). MRX = maralixibat; PLA = placebo.

[0060] **Figure 19** provides a bar graph showing mean change from baseline (BL) in sBA levels observed in the ICONIC clinical study.

[0061] **Figures 20A and 20B** demonstrate improvements in ITCHRO(Obs) scores maintained during randomized withdrawal with maralixibat in participants in the ICONIC clinical study**. Fig. 20A** shows mean change from baseline in ITCHRO(OBS) score for participants over time. **Fig 20B** shows a plot of ITCHRO(OBS) score for participants during a placebo-controlled withdrawal period.

[0062] **Figures 21A and 21B** demonstrates improvements from baseline in clinician scratch scale (CSS) scores throughout the ICONIC clinical study. **Fig. 21A** shows proportions of total patients having indicated CSS scores at baseline, week 18, and week 48. **Fig. 21B** shows proportions of total patients administered maralixibat or placebo having indicated CSS scores during a placebo-controlled withdrawal period at week 22.

[0063] **Figure 22** shows change from baseline (BL) in CSS score for participants in the ICONIC clinical study at week 48 and at week 191.

[0064] **Figures 23A-23D** provide plots of weekly average ITCHRO(OBS) score over time for participants in the ICONIC clinical study during the core study and during the extension. **Fig. 23A** provides a scatter plot showing average ITCHRO(OBS) score over time. **Fig. 23B** shows that reductions in pruritus were maintained in the long-term extension. Each line represents ITCHRO(OBS) scores for an individual patient. **Figs. 23C and 23D** show that reductions in pruritus were maintinaed with maralixibat but not with switch to placebo withdrawal period (indicated by boxed area of the plot). Each line represents ITCHRO(OBS) scores for an individual patient. MRX = maralixibat; PLA = placebo. N = number of participants measured at an indicated timepoint.

[0065] **Figure 24** shows change from baseline (BL) in ITCHRO(OBS) score at 48 weeks and at 193 weeks for participants in the ICONIC clinical study.

[0066] **Figure 25** provides a bar graph showing proportion of study days with ITCHRO(OBS) score ≤ 1 across all participants (%) in the ICONIC clinical during administration of placebo and during administration of maralixibat.

[0067] **Figure 26** shows a plot of HRQoL scores over time for patients participating in the ICONIC clinical study. HRQoL scores were measured as PEDSQL scores.

[0068] **Figure 27** provides a bar graph showing change from baseline (BL) in PEDSQL fatigue scale score (scale of 0-100) at week 48 and at week 191 for participants in the ICONIC clinical study. n = number of participants represented at an indicated time point.

[0069] **Figure 28** shows a plot of Clinician Xanthoma Scale scores over time for patients participating in the ICONIC clinical study.

[0070] **Figure 29** provides a bar graph showing change from baseline (BL) in clinician xanthoma scale score for participants in the ICONIC clinical study at week 48 and at week 191.

[0071] **Figure 30** provides a scatter plot showing serum concentrations of indicators of liver function over time for participants in the ICONIC clinical study. GGT, gamma-glutamyl transpeptidase.

[0072] **Figure 31** shows a plot of percent change from baseline in sBA against ITCHRO(OBS) weekly morning average score change from baseline for participants in the ICONIC clinical study at week 48.

[0073] **Figure 32A-32H** show lattice plots for each participant (identified by subject number above each plot) in the ICONIC clinical study through week 48. **Figs. 32A-32H** show lattice plots of sBA concentration (blue; left axis; µmol/L) and ITCHRO(OBS) weekly average score (red; right axis) over time (lower axis) for each participant in the ICONIC clinical study. **Figs. 32A** and **32D** show lattice plots for patients in an MRX-MRX-MRX study group, which includes only those patients administered maralixibat before, during, and after a placebo-controlled drug-withdrawal period of the ICONIC clinical study. **Figs. 32E** and **32H** show lattice plots for patients in an MRX-Placebo-MRX study group, which includes only those patients administered maralixibat before, placebo during, and maralixibat again after the placebo-controlled drug-withdrawal period. Patient 090004 did not have post-baseline assessments done, so the baseline datapoint is not visible in a plot.

[0074] **Figure 33** shows a scatter plot of mean change from baseline in height Z-score over time for all participants in the ICONIC clinical study. The number of patients (N) measured at each data point is indicated beneath the x-axis. BL = baseline.

[0075] **Figure 34** shows a scatter plot of mean change from baseline in height Z-score over time for participants in the ICONIC clinical study who consented to a long-term extension of the ICONIC clinical study and made it to approximately four years as participants in the study (n=15). The number of patients (N) measured at each data point is indicated beneath the x-axis. BL = baseline.

[0076] **Figure 35** shows a scatter plot of mean change from baseline in weight Z-score over time for all participants in the ICONIC clinical study (n=31). The number of patients (N) measured at each data point is indicated beneath the x-axis. BL = baseline.

[0077] **Figure 36** shows a scatter plot of mean change from baseline in height Z-score over time for participants in the ICONIC clinical study who consented to a long-term extension of the ICONIC clinical study and made it to approximately four years as participants in the study (n=15). The number of patients (N) measured at each data point is indicated beneath the x-axis. BL = baseline.

DETAILED DESCRIPTION

[0078] 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.

[0079] 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 the hydrocarbon chain is shortened by three carbon atoms resulting in a carboxyl group at the end of the chain. The most common bile acids are cholic acid and chenodeoxycholic acid (the "primary bile acids"). Before exiting the hepatocytes and forming bile, the bile acids are conjugated to either glycine (to produce glycocholic acid or glycochenodeoxycholic acid) or taurine (to produce taurocholic acid or taurochenodeoxycholic acid). The conjugated bile acids are called bile salts and their amphipathic nature makes them more efficient detergents than bile acids. Bile salts, not bile acids, are found in bile.

[0080] Bile salts are excreted by the hepatocytes into the canaliculi to form bile. The canaliculi drain into the right and left hepatic ducts and the bile flows to the gallbladder. Bile is released from the gallbladder and travels to the duodenum, where it contributes to the metabolism and degradation of fat. The bile salts are reabsorbed in the terminal ileum and transported back to the liver via the portal vein. Bile salts often undergo multiple enterohepatic circulations before being excreted via feces. A small percentage of bile salts may be reabsorbed in the proximal intestine by either passive or carrier-mediated transport processes. Most bile salts are reclaimed in the distal ileum by a sodium-dependent apically located bile acid transporter referred to as apical sodium-dependent bile acid transporter (ASBT). At the basolateral surface of the enterocyte, a truncated version of ASBT is involved in vectoral transfer of bile acids/salts into the portal circulation. Completion of the enterohepatic circulation occurs at the basolateral surface of the hepatocyte by a transport

process that is primarily mediated by a sodium-dependent bile acid transporter. Intestinal bile acid transport plays a key role in the enterohepatic circulation of bile salts. Molecular analysis of this process has recently led to important advances in understanding of the biology, physiology and pathophysiology of intestinal bile acid transport.

[0081] Within the intestinal lumen, bile acid concentrations vary, with the bulk of the reuptake occurring in the distal intestine. Described herein are certain compositions and methods that control bile acid concentrations in the intestinal lumen, thereby controlling the hepatocellular damage caused by bile acid accumulation in the liver.

Classes of Cholestasis and Cholestatic Liver Disease

[0082] As used herein, "cholestasis" means the disease or symptoms comprising impairment of bile formation and/or bile flow. As used herein, "cholestatic liver disease" means a liver disease associated with cholestasis. Cholestatic liver diseases are often associated with jaundice, fatigue, and pruritis. Biomarkers of cholestatic liver disease include elevated serum bile acid concentrations, elevated serum alkaline phosphatase (AP), elevated gamma-glutamyltranspeptidease, elevated conjugated hyperbilirubinemia, and elevated serum cholesterol.

[0083] Cholestatic liver disease can be sorted clinicopathologically between two principal categories of obstructive, often extrahepatic, cholestasis, and nonobstructive, or intrahepatic, cholestasis. In the former, cholestasis results when bile flow is mechanically blocked, as by gallstones or tumor, or as in extrahepatic biliary atresia.

[0084] The latter group who has nonobstructive intrahepatic cholestasis in turn fall into two principal subgroups. In the first subgroup, cholestasis results when processes of bile secretion and modification, or of synthesis of constituents of bile, are caught up secondarily in hepatocellular injury so severe that nonspecific impairment of many functions can be expected, including those subserving bile formation. In the second subgroup, no presumed cause of hepatocellular injury can be identified. Cholestasis in such patients appears to result when one of the steps in bile secretion or modification, or of synthesis of constituents of bile, is constitutively damaged. Such cholestasis is considered primary.

[0085] Accordingly, provided herein are methods and compositions for stimulating epithelial proliferation and/or regeneration of intestinal lining and/or enhancement of the adaptive processes in the intestine in individuals with hypercholemia and/or a cholestatic

liver disease. In some of such embodiments, the methods comprise increasing bile acid concentrations and/or GLP-2 concentrations in the intestinal lumen.

[0086] Increased levels of bile acids, and elevated levels of AP (alkaline phosphatase), LAP (leukocyte alkaline phosphatase), gamma GT (gamma-glutamyl transpeptidase), and 5 '-nucleotidase are biochemical hallmarks of cholestasis and cholestatic liver disease. Accordingly, provided herein are methods and compositions for stimulating epithelial proliferation and/or regeneration of intestinal lining and/or enhancement of the adaptive processes in the intestine in individuals with hypercholemia, and elevated levels of AP (alkaline phosphatase), LAP (leukocyte alkaline phosphatase), gamma GT (gamma-glutamyl transpeptidase or GGT), and/or 5 '-nucleotidase. In some of such embodiments, the methods comprise increasing bile acid concentrations in the intestinal lumen. Further provided herein, are methods and compositions for reducing hypercholemia, and elevated levels of AP (alkaline phosphatase), LAP (leukocyte alkaline phosphatase), gamma GT (gamma-glutamyl transpeptidase), and 5 '-nucleotidase comprising reducing overall serum bile acid load by excreting bile acid in the feces.

[0087] Pruritus is often associated with hypercholemia and cholestatic liver diseases. It has been suggested that pruritus results from bile salts acting on peripheral pain afferent nerves. The degree of pruritus varies with the individual (i.e., some individuals are more sensitive to elevated levels of bile acids/salts).

[0088] Administration of agents that reduce serum bile acid concentrations has been shown to reduce pruritus in certain individuals. Accordingly, provided herein are methods and compositions for stimulating epithelial proliferation and/or regeneration of intestinal lining and/or enhancement of the adaptive processes in the intestine in individuals with pruritus. In some of such embodiments, the methods comprise increasing bile acid concentrations in the intestinal lumen. Further provided herein, are methods and compositions for treating pruritus comprising reducing overall serum bile acid load by excreting bile acid in the feces.

[0089] Another symptom of hypercholemia and cholestatic liver disease is the increase in serum concentration of conjugated bilirubin. Elevated serum concentrations of conjugated bilirubin result in jaundice and dark urine. The magnitude of elevation is not diagnostically important as no relationship has been established between serum levels of conjugated bilirubin and the severity of hypercholemia and cholestatic liver disease. Conjugated bilirubin concentration rarely exceeds 30 mg/dL. Accordingly, provided herein are methods and compositions for stimulating epithelial proliferation and/or regeneration of intestinal lining

and/or enhancement of the adaptive processes in the intestine in individuals with elevated serum concentrations of conjugated bilirubin. In some of such embodiments, the methods comprise increasing bile acid concentrations in the intestinal lumen. Further provided herein, are methods and compositions for treating elevated serum concentrations of conjugated bilirubin comprising reducing overall serum bile acid load by excreting bile acid in the feces.

[0090] Increased serum concentration of nonconjugated bilirubin is also considered diagnostic of hypercholemia and cholestatic liver disease. Portions of serum bilirubin and covalently bound to albumin (delta bilirubin or biliprotein). This fraction may account for a large proportion of total bilirubin in patients with cholestatic jaundice. The presence of large quantities of delta bilirubin indicates long-standing cholestasis. Delta bilirubin in cord blood or the blood of a newborn is indicative of cholestasis/cholestatic liver disease that antedates birth. Accordingly, provided herein are methods and compositions for stimulating epithelial proliferation and/or regeneration of intestinal lining and/or enhancement of the adaptive processes in the intestine in individuals with elevated serum concentrations of nonconjugated bilirubin or delta bilirubin. In some of such embodiments, the methods comprise increasing bile acid concentrations in the intestinal lumen. Further provided herein, are methods and compositions for treating elevated serum concentrations of nonconjugated bilirubin and delta bilirubin comprising reducing overall serum bile acid load by excreting bile acid in the feces.

[0091] Cholestasis and cholestatic liver disease results in hypercholemia. During metabolic cholestasis, the hepatocytes retains bile salts. Bile salts are regurgitated from the hepatocyte into the serum, which results in an increase in the concentration of bile salts in the peripheral circulation. Furthermore, the uptake of bile salts entering the liver in portal vein blood is inefficient, which results in spillage of bile salts into the peripheral circulation. Accordingly, provided herein are methods and compositions for stimulating epithelial proliferation and/or regeneration of intestinal lining and/or enhancement of the adaptive processes in the intestine in individuals with hypercholemia. In some of such embodiments, the methods comprise increasing bile acid concentrations in the intestinal lumen. Further provided herein, are methods and compositions for treating hypercholemia comprising reducing overall serum bile acid load by excreting bile acid in the feces.

[0092] Hyperlipidemia is characteristic of some but not all cholestatic diseases. Serum cholesterol is elevated in cholestasis due to the decrease in circulating bile salts which contribute to the metabolism and degradation of cholesterol. Cholesterol retention is associated with an increase in membrane cholesterol content and a reduction in membrane

fluidity and membrane function. Furthermore, as bile salts are the metabolic products of cholesterol, the reduction in cholesterol metabolism results in a decrease in bile acid/salt synthesis. Serum cholesterol observed in children with cholestasis ranges between about 1,000 mg/dL and about 4,000 mg/dL. Accordingly, provided herein are methods and compositions for stimulating epithelial proliferation and/or regeneration of intestinal lining and/or enhancement of the adaptive processes in the intestine in individuals with hyperlipidemia. In some of such embodiments, the methods comprise increasing bile acid concentrations in the intestinal lumen. Further provided herein, are methods and compositions for treating hyperlipidemia comprising reducing overall serum bile acid load by excreting bile acid in the feces.

[0093] In individuals with hypercholemia and cholestatic liver diseases, xanthomas develop from the deposition of excess circulating cholesterol into the dermis. The development of xanthomas is more characteristic of obstructive cholestasis than of hepatocellular cholestasis. Planar xanthomas first occur around the eyes and then in the creases of the palms and soles, followed by the neck. Tuberous xanthomas are associated with chronic and long-term cholestasis. Accordingly, provided herein are methods and compositions for stimulating epithelial proliferation and/or regeneration of intestinal lining and/or enhancement of the adaptive processes in the intestine in individuals with xanthomas. In some of such embodiments, the methods comprise increasing bile acid concentrations in the intestinal lumen. Further provided herein, are methods and compositions for treating xanthomas comprising reducing overall serum bile acid load by excreting bile acid in the feces.

[0094] In children with chronic cholestasis, one of the major consequences of hypercholemia and cholestatic liver disease is failure to thrive. Failure to thrive is a consequence of reduced delivery of bile salts to the intestine, which contributes to inefficient digestion and absorption of fats, and reduced uptake of vitamins (vitamins E, D, K, and A are all malabsorbed in cholestasis). Furthermore, the delivery of fat into the colon can result in colonic secretion and diarrhea. Treatment of failure to thrive involves dietary substitution and supplementation with long-chain triglycerides, medium-chain triglycerides, and vitamins. Ursodeoxycholic acid, which is used to treat some cholestatic conditions, does not form mixed micelles and has no effect on fat absorption. Accordingly, provided herein are methods and compositions for stimulating epithelial proliferation and/or regeneration of intestinal lining and/or enhancement of the adaptive processes in the intestine in individuals (e.g., children) with failure to thrive. In some of such embodiments, the methods comprise

increasing bile acid concentrations in the intestinal lumen. Further provided herein, are methods and compositions for treating failure to thrive comprising reducing overall serum bile acid load by excreting bile acid in the feces.

Primary Biliary Cirrhosis (PBC)

[0095] Primary biliary cirrhosis is an autoimmune disease of the liver characterized by the destruction of the bile canaliculi. Damage to the bile cancliculi results in the build-up of bile in the liver (i.e., cholestasis). The retention of bile in the liver damages liver tissue and may lead to scarring, fibrosis, and cirrhosis. PBC usually presents in adulthood (e.g., ages 40 and over). Individuals with PBC often present with fatigue, pruritus, and/or jaundice. PBC is diagnosed if the individual has elevated AP concentrations for at least 6 months, elevated gammaGT levels, antimitochondrial antibodies (AMA) in the serum (>1 :40), and florid bile duct lesions. Serum ALT and serum AST and conjugated bilirubin may also be elevated, but these are not considered diagnostic. Cholestasis associated with PBC has been treated or ameliorated by administration of ursodeoxycholic acid (UDCA or Ursodiol). Corticosteroids (e.g., prednisone and budesonide) and immunosuppressive agents (e.g., azathioprine, cyclosporin A, methotrexate, chlorambucil and mycophenolate) have been used to treat cholestasis associated with PBC. Sulindac, bezafibrate, tamoxifen, and lamivudine have also been shown to treat or ameliorate cholestasis associated with PBC.

Progressive Familial Intrahepatic Cholestasis (PFIC)

PFIC is a rare genetic disorder that causes progressive liver disease typically leading to liver failure. In people with PFIC, liver cells are less able to secrete bile. The resulting buildup of bile causes liver disease in affected individuals. Signs and symptoms of PFIC typically begin in infancy. Patients experience severe itching, jaundice, failure to grow at the expected rate (failure to thrive), and an increasing inability of the liver to function (liver failure). The disease is estimated to affect one in every 50,000 to 100,000 births in the United States and Europe. Six types of PFIC have been genetically identified, all of which are similarly characterized by impaired bile flow and progressive liver disease.

PFIC 1

[0096] PFIC 1 (also known as, Byler disease or FICl deficiency) is associated with mutations in the ATP8B1 gene (also designated as FICl). This gene, which encodes a P-type ATPase, is located on human chromosome 18 and is also mutated in the milder phenotype, benign recurrent intrahepatic cholestasis type 1 (BRIO) and in Greenland familial cholestasis.

FICl protein is located on the canalicular membrane of the hepatocyte but within the liver it is mainly expressed in cholangiocytes. P-type ATPase appears to be an aminophospholipid transporter responsible for maintaining the enrichment of phosphatidylserine and phophatidylethanolamme on the inner leaflet of the plasma membrane in comparison of the outer leaflet. The asymmetric distribution of lipids in the membrane bilayer plays a protective role against high bile salt concentrations in the canalicular lumen. The abnormal protein function may indirectly disturb the biliary secretion of bile acids. The anomalous secretion of bile acids/salts leads to hepatocyte bile acid overload.

[0097] PFIC 1 typically presents in infants (e.g., age 6-18 months). The infants may show signs of pruritus, jaundice, abdominal distension, diarrhea, malnutrition, and shortened stature. Biochemically, individuals with PFIC 1 have elevated serum transaminases, elevated bilirubin, elevated serum bile acid levels, and low levels of gammaGT. The individual may also have liver fibrosis. Individuals with PFIC 1 typically do not have bile duct proliferation. Most individuals with PFIC 1 will develop end-stage liver disease by 10 years of age. No medical treatments have proven beneficial for the long-term treatment of PFIC 1. In order to reduce extrahepatic symptoms (e.g., malnutrition and failure to thrive), children are often administered medium chain triglycerides and fat-soluble vitamins. Ursodiol has not been demonstrated as effective in individuals with PFIC 1.

PFIC 2

[0098] PFIC 2 (also known as, Byler Syndrome or BSEP deficiency) is associated with mutations in the ABCB11 gene (also designated BSEP). The ABCB11 gene encodes the ATP-dependent canalicular bile salt export pump (BSEP) of human liver and is located on human chromosome 2. BSEP protein, expressed at the hepatocyte canalicular membrane, is the major exporter of primary bile acids/salts against extreme concentration gradients. Mutations in this protein are responsible for the decreased biliary bile salt secretion described in affected patients, leading to decreased bile flow and accumulation of bile salts inside the hepatocyte with ongoing severe hepatocellular damage.

[0099] PFIC 2 typically presents in infants (e.g., age 6-18 months). The infants may show signs of pruritus. Biochemically, individuals with PFIC 2 have elevated serum transaminases, elevated bilirubin, elevated serum bile acid levels, and low levels of gammaGT. The individual may also have portal inflammation and giant cell hepatitis. Further, individuals often develop hepatocellular carcinoma. No medical treatments have proven beneficial for the long-term treatment of PFIC 2. In order to reduce extrahepatic symptoms (e.g., malnutrition

and failure to thrive), children are often administered medium chain triglycerides and fat-soluble vitamins. The PFIC 2 patient population accounts for approximately 60% of the PFIC population.

PFIC 3

[00100] PFIC 3 (also known as MDR3 deficiency) is caused by a genetic defect in the ABCB4 gene (also designated MDR3) located on chromosome 7. Class III Multidrug Resistance (MDR3) P-glycoprotein (P-gp), is a phospholipid translocator involved in biliary phospholipid (phosphatidylcholine) excretion in the canlicular membrane of the hepatocyte. PFIC 3 results from the toxicity of bile in which detergent bile salts are not inactivated by phospholipids, leading to bile canaliculi and biliary epithelium injuries.

[00101] PFIC 3 also presents in early childhood. As opposed to PFIC 1 and PFIC 2, individuals have elevated gammaGT levels. Individuals also have portal inflammation, fibrosis, cirrhosis, and massive bile duct proliferation. Individuals may also develop intrahepatic gallstone disease. Ursodiol has been effective in treating or ameliorating PFIC 3.

Benign Recurrent Intrahepatic Cholestasis (BRIC)

BRIC 1

[00102] BRIC1 is caused by a genetic defect of the FICl protein in the canalicular membrane of hepatocytes. BRIC1 is typically associated with normal serum cholesterol and γ-glutamyltranspeptidase levels, but elevated serum bile salts. Residual FICl expression and function is associated with BRICl . Despite recurrent attacks of cholestasis or cholestatic liver disease, there is no progression to chronic liver disease in a majority of patients. During the attacks, the patients are severely jaundiced and have pruritis, steatorrhea, and weight loss. Some patients also have renal stones, pancreatitis, and diabetes.

BRIC 2

[00103] BRIC2 is caused by mutations in ABCB11, leading to defective BSEP expression and/or function in the canalicular membrane of hepatocytes.

BRIC 3

[00104] BRIC3 is related to the defective expression and/or function of MDR3 in the canalicular membrane of hepatocytes. Patients with MDR3 deficiency usually display elevated serum γ-glutamyltranspeptidase levels in the presence of normal or slightly elevated bile acid levels.

Dubin-Johnson Syndrome (DJS)

[00105] DJS is characterized by conjugated hyperbilirubinemia due to inherited dysfunction of MRP2. Hepatic function is preserved in affected patients. Several different mutations have been associated with this condition, resulting either in the complete absence of immunohistochemically detectable MRP2 in affected patients or impaired protein maturation and sorting.

Acquired Cholestatic Disease

Primary Biliary Cirrhosis (PBC)

[00106] PBC is a chronic inflammatory hepatic disorder slowly progressing to end stage liver failure in most of the affected patients. In PBC, the inflammatory process affects predominantly the small bile ducts.

Primary Sclerosing Cholangitis (PSC)

[00107] PSC is a chronic inflammatory hepatic disorder slowly progressing to end stage liver failure in most of the affected patients. In PSC inflammation, fibrosis and obstruction of large and medium sized intra- and extrahepatic ductuli is predominant.

[00108] PSC is characterized by progressive cholestasis. Cholestasis can often lead to severe pruritus which significantly impairs quality of life.

Intrahepatic Cholestasis of Pregnancy (ICP)

[00109] ICP is characterized by occurrence of transient cholestasis or cholestatic liver disease in pregnant women typically occurring in the third trimester of pregnancy, when the circulating levels of estrogens are high. ICP is associated with pruritis and biochemical cholestasis or cholestatic liver disease of varying severity and constitutes a risk factor for prematurity and intrauterine fetal death. A genetic predisposition has been suspected based upon the strong regional clustering, the higher prevalence in female family members of patients with ICP and the susceptibility of ICP patients to develop intrahepatic cholestasis or cholestatic liver disease under other hormonal challenges such as oral contraception. A heterogeneous state for an MDR3 gene defect may represent a genetic predisposition.

Gallstone disease

[00110] Gallstone disease is one of the most common and costly of all digestive diseases with a prevalence of up to 17% in Caucasian women. Cholesterol containing gallstones are the major form of gallstones and supersaturation of bile with cholesterol is therefore a

prerequisite for gallstone formation. ABCB4 mutations may be involved in the pathogenesis of cholesterol gallstone disease.

Drug induced cholestasis

[00111] Inhibition of BSEP function by drugs is an important mechanism of drug-induced cholestasis, leading to the hepatic accumulation of bile salts and subsequent liver cell damage. Several drugs have been implicated in BSEP inhibition. Most of these drugs, such as rifampicin, cyclosporine, glibenclamide, or troglitazone directly cis-inhibit ATP-dependent taurocholate transport in a competitive manner, while estrogen and progesterone metabolites indirectly trans-inhibits BSEP after secretion into the bile canaliculus by Mrp2. Alternatively, drug-mediated stimulation of MRP2 can promote cholestasis or cholestatic liver disease by changing bile composition.

Total parenteral nutrition associated cholestasis

[00112] TPNAC is one of the most serious clinical scenarios where cholestasis or cholestatic liver disease occurs rapidly and is highly linked with early death. Infants, who are usually premature and who have had gut resections are dependent upon TPN for growth and frequently develop cholestasis or cholestatic liver disease that rapidly progresses to fibrosis, cirrhosis, and portal hypertension, usually before 6 months of life. The degree of cholestasis or cholestatic liver disease and chance of survival in these infants have been linked to the number of septic episodes, likely initiated by recurrent bacterial translocation across their gut mucosa. Although there are also cholestatic effects from the intravenous formulation in these infants, septic mediators likely contribute the most to altered hepatic function.

Alagille syndrome (ALGS)

[00113] Alagille syndrome is a genetic disorder that affects the liver and other organs. ALGS is also known as syndromic intrahepatic bile duct paucity or arteriohepatic dysplasia. ALGS is a rare genetic disorder in which bile ducts are abnormally narrow, malfomrmed, and reduced in number, which leads to bile accumulation in the liver and ultimately progressive liver disease. ALGS is autosomal dominant, caused by mutations in JAG1 (> 90% of cases) or NOTCH2. The estimated incidence of ALGS is one in every 30,000 or 50,000 births in the United States and Europe. In patients with ALGS, multiple organ systems may be affected by the mutation, including the liver, heart, kidneys and central nervous system. The accumulation of bile acids prevents the liver from working properly to eliminate waste from the bloodstream and leads to progressive liver disease that ultimately requires liver

transplantation in 15% to 47% of patients. Signs and symptoms arising from liver damage in ALGS may include jaundice, pruritus and xanthomas, and decreased growth. The pruritus experienced by patients with ALGS is among the most severe in any chronic liver disease and is present in most affected children by the third year of life.

[00114] ALGS often presents during infancy (e.g., age 6-18 months) through early childhood (e.g., age 3-5 years) and may stabilize after the age of 10. Symptoms may include chronic progressive cholestasis, ductopenia, jaundice, pruritus, xanthomas, congenital heart problems, paucity of intrahepatic bile ducts, poor linear growth, hormone resistance, posterior embryotoxon, Axenfeld anomaly, retinitis pigmentosa, pupillary abnormalities, cardiac murmur, atrial septal defect, ventricular septal defect, patent ductus arteriosus, and Tetralogy of Fallot. Individuals diagnosed with Alagille syndrome have been treated with ursodiol, hydroxyzine, cholestyramine, rifampicin, and phenobarbitol. Due to a reduced ability to absorb fat-soluble vitamins, individuals with Alagille Syndrome are further administered high dose multivitamins.

Biliary atresia

[00115] Biliary atresia is a life-threatening condition in infants in which the bile ducts inside or outside the liver do not have normal openings. With biliary atresia, bile becomes trapped, builds up, and damages the liver. The damage leads to scarring, loss of liver tissue, and cirrhosis. Without treatment, the liver eventually fails, and the infant needs a liver transplant to stay alive. The two types of biliary atresia are fetal and perinatal. Fetal biliary atresia appears while the baby is in the womb. Perinatal biliary atresia is much more common and does not become evident until 2 to 4 weeks after birth.

Post-Kasai biliary atresia

[00116] Biliary atresia is treated with surgery called the Kasai procedure or a liver transplant. The Kasai procedure is usually the first treatment for biliary atresia. During a Kasai procedure, the pediatric surgeon removes the infant's damaged bile ducts and brings up a loop of intestine to replace them. While the Kasai procedure can restore bile flow and correct many problems caused by biliary atresia, the surgery doesn't cure biliary atresia. If the Kasai procedure is not successful, infants usually need a liver transplant within 1 to 2 years. Even after a successful surgery, most infants with biliary atresia slowly develop cirrhosis over the years and require a liver transplant by adulthood. Possible complications after the Kasai procedure include ascites, bacterial cholangitis, portal hypertension, and pruritis.

Post liver transplantation biliary atresia

[00117] If the atresia is complete, liver transplantation is the only option. Although liver transplantation is generally successful at treating biliary atresia, liver transplantation may have complications such as organ rejection. Also, a donor liver may not become available. Further, in some patients, liver transplantation may not be successful at curing biliary atresia.

Xanthoma

[00118] Xanthoma is a skin condition associated with cholestatic liver diseases, in which certain fats build up under the surface of the skin. Cholestasis results in several disturbances of lipid metabolism resulting in formation of an abnormal lipid particle in the blood called lipoprotein X. Lipoprotein X is formed by regurgitation of bile lipids into the blood from the liver and does not bind to the LDL receptor to deliver cholesterol to cells throughout the body as does normal LDL. Lipoprotein X increases liver cholesterol production by fivefold and blocks normal removal of lipoprotein particles from the blood by the liver.

General Definitions

[00119] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

[00120] As used in this specification and the appended claims, the singular forms "a", "an", and "the" include plural references unless the context clearly dictates otherwise. Thus, for example, a reference to "a method" includes one or more methods, and/or steps of the type described herein and/or which will become apparent to those persons skilled in the art upon reading this disclosure.

[00121] The term "baseline" or "pre-administration baseline," as used herein, refers to information gathered at the beginning of a study or an initial known value which is used for comparison with later data. A baseline is an initial measurement of a measurable condition that is taken at an early time point and used for comparison over time to look for changes in the measurable condition. For example, serum bile acid concentration in a patient before administration of a drug (baseline) and after administration of the drug. Baseline is an observation or value that represents the normal or beginning level of a measurable quality, used for comparison with values representing response to intervention or an environmental stimulus. The baseline is time "zero", before participants in a study receive an experimental

agent or intervention, or negative control. For example, “baseline” may refer in some instances 1) to the state of a measurable quantity just prior to the initiation of a clinical study or 2) the state of a measurable quantity just prior to altering a dosage level or composition administered to a patient from a first dosage level or composition to a second dosage level or composition.

[00122] The terms “level” and “concentration,” as used herein, are used interchangeably. For example, “high serum levels of bilirubin” may alternatively be phrased “high serum concentrations of bilirubin.”

[00123] The terms “normalized” or “normal range,” as used herein, indicates age-specific values that are within a range corresponding to a healthy individual (i.e., normal or normalized values). For example, the phrase “serum bilirubin concentratins were normalized within three weeks” means that serum bilirubin concentrations fell within a range known in the art to correspond to that of a healthy individual (i.e., within a normal and not e.g. an elevated range) within three weeks. In various embodiments, a normalized serum bilirubin concentration is from about 0.1 mg/dL to about 1.2 mg/dL. In various embodiments, a normalized serum bile acid concentration is from about 0 μmol/L to about 25 μmol/L.

[00124] The terms “ITCHRO(OBS)” and “ITCHRO” (alternatively, “ItchRO(Pt)”) as used herein, are used interchangeably with the qualification that the ITCHRO(OBS) scale is used to measure severity of pruritus in children under the age of 18 and the ITCHRO scale is used to measure severity of pruritus in adults of at least 18 years of age. Therefore, where ITCHRO(OBS) scale is mentioned with regard to an adult patient, the ITCHRO scale is the scale being indicated. Similarly, whenever the ITCHRO scale is mentioned with regard to a pediatric patient, the ITCHRO(OBS) scale is usually the scale being indicated (some older children were permitted to report their own scores as ITCHRO scores. The ITCHRO(OBS) scale ranges from 0 to 4 and the ITCHRO scale ranges from 0 to 10.

[00125] The term "bile acid" or “bile acids,” as used herein, includes steroid acids (and/or the carboxylate anion thereof), and salts thereof, found in the bile of an animal (e.g., a human), including, by way of non-limiting example, cholic acid, cholate, deoxycholic acid, deoxycholate, hyodeoxycholic acid, hyodeoxycholate, glycocholic acid, glycocholate, taurocholic acid, taurocholate, chenodeoxycholic acid, ursodeoxycholic acid, ursodiol, a tauroursodeoxycholic acid, a glycoursodeoxycholic acid, a 7-B-methyl cholic acid, a methyl lithocholic acid, chenodeoxycholate, lithocholic acid, lithocolate, and the like. Taurocholic acid and/or taurocholate are referred to herein as TCA. Any reference to a bile acid used

herein includes reference to a bile acid, one and only one bile acid, one or more bile acids, or to at least one bile acid. Therefore, the terms "bile acid," "bile salt," "bile acid/salt," "bile acids," "bile salts," and "bile acids/salts" are, unless otherwise indicated, utilized interchangeably herein. Any reference to a bile acid used herein includes reference to a bile acid or a salt thereof. Furthermore, pharmaceutically acceptable bile acid esters are optionally utilized as the "bile acids" described herein, e.g., bile acids/salts conjugated to an amino acid (e.g., glycine or taurine). Other bile acid esters include, e.g., substituted or unsubstituted alkyl ester, substituted or unsubstituted heteroalkyl esters, substituted or unsubstituted aryl esters, substituted or unsubstituted heteroaryl esters, or the like. For example, the term "bile acid" includes cholic acid conjugated with either glycine or taurine: glycocholate and taurocholate, respectively (and salts thereof). Any reference to a bile acid used herein includes reference to an identical compound naturally or synthetically prepared. Furthermore, it is to be understood that any singular reference to a component (bile acid or otherwise) used herein includes reference to one and only one, one or more, or at least one of such components. Similarly, any plural reference to a component used herein includes reference to one and only one, one or more, or at least one of such components, unless otherwise noted.

[00126] The term "subject", "patient", “participant”, or "individual" are used interchangeably herein and refer to mammals and non-mammals, e.g., suffering from a disorder described herein. Examples of mammals include, but are not limited to, any member of the mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. Examples of non-mammals include, but are not limited to, birds, fish and the like. In one embodiment of the methods and compositions provided herein, the mammal is a human.

[00127] The term "about," as used herein, includes any value that is within 10% of the described value.

[00128] The term "composition," as used herein includes the disclosure of both a composition and a composition administered in a method as described herein. Furthermore, in some embodiments, the composition of the present invention is or comprises a "formulation," an oral dosage form or a rectal dosage form as described herein.

[00129] The terms "treat," "treating" or "treatment," and other grammatical equivalents as used herein, include alleviating, inhibiting or reducing symptoms, reducing or inhibiting

severity of, reducing incidence of, reducing or inhibiting recurrence of, delaying onset of, delaying recurrence of, abating or ameliorating a disease or condition symptoms, ameliorating the underlying causes of symptoms, inhibiting the disease or condition, e.g., arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition. The terms further include achieving a therapeutic benefit. By therapeutic benefit is meant eradication or amelioration of the underlying disorder being treated, and/or the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient.

[00130] The terms "effective amount" or "therapeutically effective amount" as used herein, refer to a sufficient amount of at least one agent (e.g., a therapeutically active agent) being administered which achieve a desired result in a subject or individual, e.g., to relieve to some extent one or more symptoms of a disease or condition being treated. In certain instances, the result is a reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. In certain instances, an "effective amount" for therapeutic uses is the amount of the composition comprising an agent as set forth herein required to provide a clinically significant decrease in a disease. An appropriate "effective" amount in any individual case is determined using any suitable technique, such as a dose escalation study. In some embodiments, a "therapeutically effective amount," or an "effective amount" of an ASBTI refers to a sufficient amount of an ASBTI to treat cholestasis or a cholestatic liver disease in a subject or individual.

[00131] The terms "administer," "administering", "administration," and the like, as used herein, refer to the methods that may be used to enable delivery of agents or compositions to the desired site of biological action. These methods include, but are not limited to oral routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intraperitoneal, intramuscular, intravascular or infusion), topical and rectal administration. Administration techniques that are optionally employed with the agents and methods described herein are found in sources e.g., Goodman and Gilman, The Pharmacological Basis of Therapeutics, current ed.; Pergamon; and Remington's, Pharmaceutical Sciences (current edition), Mack Publishing Co., Easton, Pa, all of which are incorporated herein by reference in their entirety for all purposes. In certain embodiments, the agents and compositions described herein are administered orally.

[00132] The term "ASBT inhibitor" refers to a compound that inhibits apical sodium-dependent bile transport or any recuperative bile salt transport. The term Apical Sodium-dependent Bile Transporter (ASBT) is used interchangeably with the term Ileal Bile Acid Transporter (IBAT).

[00133] The phrase "pharmaceutically acceptable", as used in connection with compositions of the invention, refers to molecular entities and other ingredients of such compositions that are physiologically tolerable and do not typically produce untoward reactions when administered to a mammal (e.g., a human). Preferably, as used herein, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in mammals, and more particularly in humans.

[00134] In various embodiments, pharmaceutically acceptable salts described herein include, by way of non-limiting example, a nitrate, chloride, bromide, phosphate, sulfate, acetate, hexafluorophosphate, citrate, gluconate, benzoate, propionate, butyrate, subsalicylate, maleate, laurate, malate, fumarate, succinate, tartrate, amsonate, pamoate, p-tolunenesulfonate, mesylate and the like. Furthermore, pharmaceutically acceptable salts include, by way of non-limiting example, alkaline earth metal salts (e.g., calcium or magnesium), alkali metal salts (e.g., sodium-dependent or potassium), ammonium salts and the like.

Bile Acid

[00135] Bile contains water, electrolytes and a numerous organic molecules including bile acids, cholesterol, phospholipids and bilirubin. Bile is secreted from the liver and stored in the gall bladder, and upon gall bladder contraction, due to ingestion of a fatty meal, bile passes through the bile duct into the intestine. Bile acids/salts are critical for digestion and absorption of fats and fat-soluble vitamins in the small intestine. Adult humans produce 400 to 800 mL of bile daily. The secretion of bile can be considered to occur in two stages. Initially, hepatocytes secrete bile into canaliculi, from which it flows into bile ducts and this hepatic bile contains large quantities of bile acids, cholesterol and other organic molecules. Then, as bile flows through the bile ducts, it is modified by addition of a watery, bicarbonate -rich secretion from ductal epithelial cells. Bile is concentrated, typically five-fold, during storage in the gall bladder.

[00136] The flow of bile is lowest during fasting, and a majority of that is diverted into the gallbladder for concentration. When chyme from an ingested meal enters the small intestine, acid and partially digested fats and proteins stimulate secretion of cholecystokinin and secretin, both of which are important for secretion and flow of bile. Cholecystokinin (cholecysto = gallbladder and kinin = movement) is a hormone which stimulates contractions of the gallbladder and common bile duct, resulting in delivery of bile into the gut. The most potent stimulus for release of cholecystokinin is the presence of fat in the duodenum. Secretin is a hormone secreted in response to acid in the duodenum, and it simulates biliary duct cells to secrete bicarbonate and water, which expands the volume of bile and increases its flow out into the intestine.

[00137] Bile acids/salts are derivatives of cholesterol. Cholesterol, ingested as part of the diet or derived from hepatic synthesis, are converted into bile acids/salts in the hepatocyte. Examples of such bile acids/salts include cholic and chenodeoxycholic acids, which are then conjugated to an amino acid (such as glycine or taurine) to yield the conjugated form that is actively secreted into cannaliculi. The most abundant of the bile salts in humans are cholate and deoxycholate, and they are normally conjugated with either glycine or taurine to give glycocholate or taurocholate respectively.

[00138] Free cholesterol is virtually insoluble in aqueous solutions, however in bile it is made soluble by the presence of bile acids/salts and lipids. Hepatic synthesis of bile acids/salts accounts for the majority of cholesterol breakdown in the body. In humans, roughly 500 mg of cholesterol are converted to bile acids/salts and eliminated in bile every day. Therefore, secretion into bile is a major route for elimination of cholesterol. Large amounts of bile acids/salts are secreted into the intestine every day, but only relatively small quantities are lost from the body. This is because approximately 95% of the bile acids/salts delivered to the duodenum are absorbed back into blood within the ileum, by a process is known as "Enterohepatic Recirculation".

[00139] Venous blood from the ileum goes straight into the portal vein, and hence through the sinusoids of the liver. Hepatocytes extract bile acids/salts very efficiently from sinusoidal blood, and little escapes the healthy liver into systemic circulation. Bile acids/salts are then transported across the hepatocytes to be resecreted into canaliculi. The net effect of this enterohepatic recirculation is that each bile salt molecule is reused about 20 times, often two or three times during a single digestive phase. Bile biosynthesis represents the major metabolic fate of cholesterol, accounting for more than half of the approximate 800 mg/day

of cholesterol that an average adult uses up in metabolic processes. In comparison, steroid hormone biosynthesis consumes only about 50 mg of cholesterol per day. Much more that 400 mg of bile salts is required and secreted into the intestine per day, and this is achieved by re-cycling the bile salts. Most of the bile salts secreted into the upper region of the small intestine are absorbed along with the dietary lipids that they emulsified at the lower end of the small intestine. They are separated from the dietary lipid and returned to the liver for re-use. Recycling thus enables 20-30 g of bile salts to be secreted into the small intestine each day.

[00140] Bile acids/salts are amphipathic, with the cholesterol-derived portion containing both hydrophobic (lipid soluble) and polar (hydrophilic) moieties while the amino acid conjugate is generally polar and hydrophilic. This amphipathic nature enables bile acids/salts to carry out two important functions: emulsification of lipid aggregates and solubilization and transport of lipids in an aqueous environment. Bile acids/salts have detergent action on particles of dietary fat which causes fat globules to break down or to be emulsified. Emulsification is important since it greatly increases the surface area of fat available for digestion by lipases which cannot access the inside of lipid droplets. Furthermore, bile acids/salts are lipid carriers and are able to solubilize many lipids by forming micelles and are critical for transport and absorption of the fat-soluble vitamins.

[00141] The term "non-systemic" or "minimally absorbed," as used herein, refers to low systemic bioavailability and/or absorption of an administered compound. In some embodiments, a non-systemic compound is a compound that is substantially not absorbed systemically. In some embodiments, ASBTI compositions described herein deliver the ASBTI to the distal ileum, colon, and/or rectum and not systemically (e.g., a substantial portion of the ASBTI is not systemically absorbed. In some embodiments, the systemic absorption of a non-systemic compound is <0.1%, <0.3%, <0.5%, <0.6%, <0.7%, <0.8%, <0.9%, <1%, <1.5%, <2%, <3%, or < 5 % of the administered dose (wt. % or mol %). In some embodiments, the systemic absorption of a non-systemic compound is < 10 % of the administered dose. In some embodiments, the systemic absorption of a non-systemic compound is < 15 % of the administered dose. In some embodiments, the systemic absorption of a non-systemic compound is < 25% of the administered dose. In an alternative approach, a non-systemic ASBTI is a compound that has lower systemic bioavailability relative to the systemic bioavailability of a systemic ASBTI (e.g., compound 100A, 100C). In some embodiments, the bioavailability of a non-systemic ASBTI described herein is < 30%,

< 40%, < 50%, < 60%, or < 70% of the bioavailability of a systemic ASBTI (e.g., compound 100A, 100C).

[00142] In another alternative approach, compositions described herein are formulated to deliver < 10 % of the administered dose of the ASBTI systemically. In some embodiments, the compositions described herein are formulated to deliver < 20 % of the administered dose of the ASBTI systemically. In some embodiments, the compositions described herein are formulated to deliver < 30 % of the administered dose of the ASBTI systemically. In some embodiments, the compositions described herein are formulated to deliver < 40 % of the administered dose of the ASBTI systemically. In some embodiments, the compositions described herein are formulated to deliver < 50 % of the administered dose of the ASBTI systemically. In some embodiments, the compositions described herein are formulated to deliver < 60 % of the administered dose of the ASBTI systemically. In some embodiments, the compositions described herein are formulated to deliver < 70 % of the administered dose of the ASBTI systemically. In some embodiments, systemic absorption is determined in any suitable manner, including the total circulating amount, the amount cleared after administration, or the like.

[00143] The term "optionally substituted" or "substituted" means that the referenced group substituted with one or more additional group(s). In certain embodiments, the one or more additional group(s) are individually and independently selected from amide, ester, alkyl, cycloalkyl, heteroalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, ester, alkylsulfone, arylsulfone, cyano, halo, alkoyl, alkoyloxo, isocyanato, thiocyanato, isothiocyanato, nitro, haloalkyl, haloalkoxy, fluoroalkyl, amino, alkyl-amino, dialkyl-amino, amido.

[00144] An "alkyl" group refers to an aliphatic hydrocarbon group. Reference to an alkyl group includes "saturated alkyl" and/or "unsaturated alkyl". The alkyl group, whether saturated or unsaturated, includes branched, straight chain, or cyclic groups. By way of example only, alkyl includes methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, pentyl, iso-pentyl, neo-pentyl, and hexyl. In some embodiments, alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, hexyl, ethenyl, propenyl, butenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like. A "lower alkyl" is a C_1-C_6 alkyl. A "heteroalkyl" group substitutes any one of the carbons of the alkyl group with a heteroatom having the appropriate number of hydrogen atoms attached (e.g., a CH_2 group to an NH group or an O group).

[00145] The term "alkylene" refers to a divalent alkyl radical. Any of the above mentioned monovalent alkyl groups may be an alkylene by abstraction of a second hydrogen atom from the alkyl. In one aspect, an alkelene is a C_1-C_{10}alkylene. In another apsect, an alkylene is a C_1-C_6alkylene. Typical alkylene groups include, but are not limited to, -CH_2-, -$CH(CH_3)$-, -$C(CH_3)_2$-, -CH_2CH_2-, -$CH_2CH(CH_3)$-, -$CH_2C(CH_3)_2$-, -$CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2$-, and the like.

[00146] An "alkoxy" group refers to a (alkyl)O- group, where alkyl is as defined herein.

[00147] The term "alkylamine" refers to the –$N(alkyl)_xH_y$ group, wherein alkyl is as defined herein and x and y are selected from the group x=1, y=1 and x=2, y=0. When x=2, the alkyl groups, taken together with the nitrogen to which they are attached, optionally form a cyclic ring system.

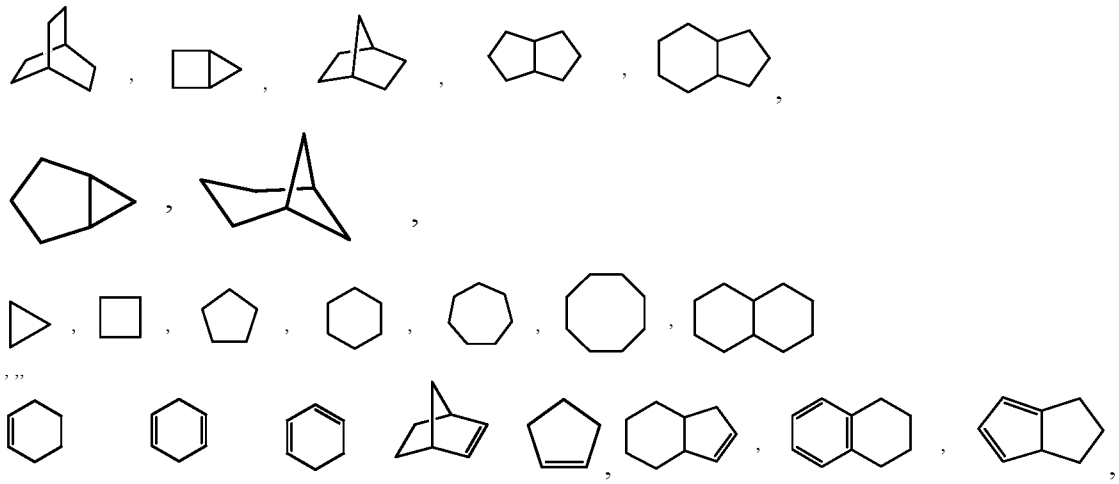
[00148] An "amide" is a chemical moiety with formula -C(O)NHR or -NHC(O)R, where R is selected from alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon).

[00149] The term "ester" refers to a chemical moiety with formula –C(=O)OR, where R is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl and heteroalicyclic.

[00150] As used herein, the term "aryl" refers to an aromatic ring wherein each of the atoms forming the ring is a carbon atom. Aryl rings described herein include rings having five, six, seven, eight, nine, or more than nine carbon atoms. Aryl groups are optionally substituted. Examples of aryl groups include, but are not limited to phenyl, and naphthalenyl.

[00151] The term "aromatic" refers to a planar ring having a delocalized π-electron system containing 4n+2 π electrons, where n is an integer. Aromatic rings can be formed from five, six, seven, eight, nine, ten, or more than ten atoms. Aromatics are optionally substituted. The term "aromatic" includes both carbocyclic aryl ("aryl", *e.g.*, phenyl) and heterocyclic aryl (or "heteroaryl" or "heteroaromatic") groups (*e.g.*, pyridine). The term includes monocyclic or fused-ring polycyclic (*i.e.*, rings which share adjacent pairs of carbon atoms) groups.

[00152] The term "cycloalkyl" refers to a monocyclic or polycyclic non-aromatic radical, wherein each of the atoms forming the ring (i.e. skeletal atoms) is a carbon atom. In various embodiments, cycloalkyls are saturated, or partially unsaturated. In some embodiments, cycloalkyls are fused with an aromatic ring. Cycloalkyl groups include groups having from 3 to 10 ring atoms. Illustrative examples of cycloalkyl groups include, but are not limited to, the following moieties:

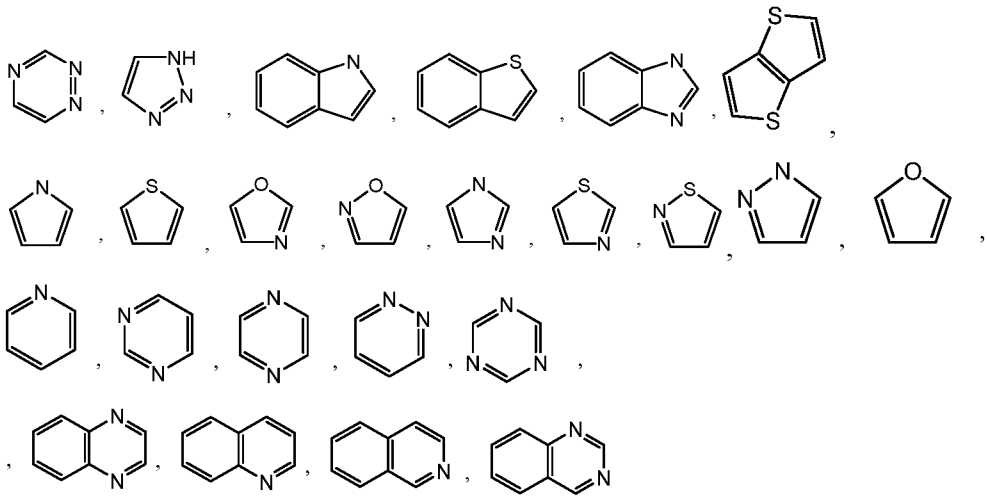


[00153] and the like. Monocyclic cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

[00154] The term "heterocyclo" refers to heteroaromatic and heteroalicyclic groups containing one to four ring heteroatoms each selected from O, S and N. In certain instances, each heterocyclic group has from 4 to 10 atoms in its ring system, and with the proviso that the ring of said group does not contain two adjacent O or S atoms. Non-aromatic heterocyclic groups include groups having 3 atoms in their ring system, but aromatic heterocyclic groups must have at least 5 atoms in their ring system. The heterocyclic groups include benzo-fused ring systems. An example of a 3-membered heterocyclic group is aziridinyl (derived from aziridine). An example of a 4-membered heterocyclic group is azetidinyl (derived from azetidine). An example of a 5-membered heterocyclic group is thiazolyl. An example of a 6-membered heterocyclic group is pyridyl, and an example of a 10-membered heterocyclic group is quinolinyl. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, aziridinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl and quinolizinyl. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl,

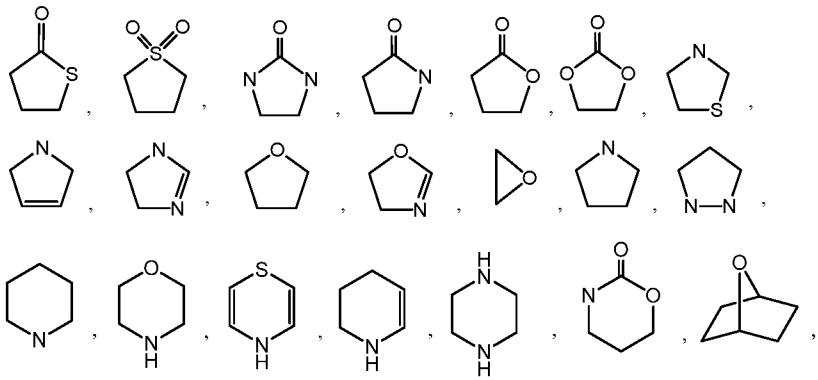
indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl.

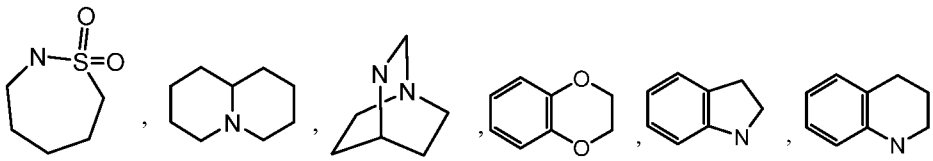
[00155] The terms "heteroaryl" or, alternatively, "heteroaromatic" refers to an aryl group that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur. An *N*-containing "heteroaromatic" or "heteroaryl" moiety refers to an aromatic group in which at least one of the skeletal atoms of the ring is a nitrogen atom. In certain embodiments, heteroaryl groups are monocyclic or polycyclic. Illustrative examples of heteroaryl groups include the following moieties:



and the like.

[00156] A "heteroalicyclic" group or "heterocyclo" group refers to a cycloalkyl group, wherein at least one skeletal ring atom is a heteroatom selected from nitrogen, oxygen and sulfur. In various embodiments, the radicals are with an aryl or heteroaryl. Illustrative examples of heterocyclo groups, also referred to as non-aromatic heterocycles, include:





and the like. The term heteroalicyclic also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides and the oligosaccharides.

[00157] The term "halo" or, alternatively, "halogen" means fluoro, chloro, bromo and iodo.

[00158] The terms "haloalkyl," and "haloalkoxy" include alkyl and alkoxy structures that are substituted with one or more halogens. In embodiments, where more than one halogen is included in the group, the halogens are the same or they are different. The terms "fluoroalkyl" and "fluoroalkoxy" include haloalkyl and haloalkoxy groups, respectively, in which the halo is fluorine.

[00159] The term "heteroalkyl" include optionally substituted alkyl, alkenyl and alkynyl radicals which have one or more skeletal chain atoms selected from an atom other than carbon, e.g., oxygen, nitrogen, sulfur, phosphorus, silicon, or combinations thereof. In certain embodiments, the heteroatom(s) is placed at any interior position of the heteroalkyl group. Examples include, but are not limited to, $-CH_2-O-CH_3$, $-CH_2-CH_2-O-CH_3$, $-CH_2-NH-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-N(CH_3)-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2,-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, and $-CH=CH-N(CH_3)-CH_3$. In some embodiments, up to two heteroatoms are consecutive, such as, by way of example, $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$.

[00160] A "cyano" group refers to a -CN group.

[00161] An "isocyanato" group refers to a -NCO group.

[00162] A "thiocyanato" group refers to a -CNS group.

[00163] An "isothiocyanato" group refers to a -NCS group.

[00164] "Alkoyloxy" refers to a RC(=O)O- group.

[00165] "Alkoyl" refers to a RC(=O)- group.

[00166] The term "modulate," as used herein refers to having some affect on (e.g., increasing, enhancing or maintaining a certain level).

[00167] The term "optionally substituted" or "substituted" means that the referenced group may be substituted with one or more additional group(s) individually and independently selected from C_1-C_6alkyl, C_3-C_8cycloalkyl, aryl, heteroaryl, C_2-C_6heteroalicyclic, hydroxy, C_1-C_6alkoxy, aryloxy, arylalkoxy, aralkyloxy, arylalkyloxy, C_1-C_6alkylthio, arylthio, C_1-

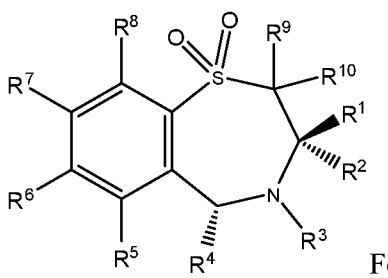
C_6alkylsulfoxide, arylsulfoxide, C_1-C_6alkylsulfone, arylsulfone, cyano, halo, C_2-C_8acyl, C_2-C_8acyloxy, nitro, C_1-C_6haloalkyl, C_1-C_6fluoroalkyl, and amino, including C_1-C_6alkylamino, and the protected derivatives thereof. By way of example, an optional substituents may be L^sR^s, wherein each L^s is independently selected from a bond, -O-, -C(=O)-, -S-, -S(=O)-, -$S(=O)_2$-, -NH-, -NHC(=O)-, -C(=O)NH-, $S(=O)_2NH$-, -$NHS(=O)_2$-, -OC(=O)NH-, -NHC(=O)O-, -(C_1-C_6alkyl)-, or -(C_2-C_6alkenyl)-; and each R^s is independently selected from H, (C_1-C_4alkyl), (C_3-C_8cycloalkyl), heteroaryl, aryl, and C_1-C_6heteroalkyl. Optionally substituted non-aromatic groups may be substituted with one or more oxo (=O). The protecting groups that may form the protective derivatives of the above substituents are known to those of skill in the art and may be found in references such as Greene and Wuts, above. In some embodiments, alkyl groups described herein are optionally substituted with an O that is connected to two adjacent carbon atoms (i.e., forming an epoxide).

ASBT Inhibitors

[00168] In various embodiments of methods of the present invention, ASBT inhibitors are administered to a subject. ASBT inhibitors (ASBTIs) reduce or inhibit bile acid recycling in the distal gastrointestinal (GI) tract, including the distal ileum, the colon and/or the rectum. Inhibition of the apical sodium-dependent bile acid transport interrupts the enterohepatic circulation of bile acids and results in more bile acids being excreted in the feces, see Fig. 1, leading to lower levels of bile acids systemically, thereby reducing bile acid mediated liver damage and related effects and complications. In certain embodiments, the ASBTIs are systemically absorbed. In certain embodiments, the ASBTIs are not systemically absorbed. In some embodiments, ASBTIs described herein are modified or substituted (e.g., with a –L-K group) to be non-systemic. In certain embodiments, any ASBT inhibitor is modified or substituted with one or more charged groups (e.g., K) and optionally, one or more linker (e.g., L), wherein L and K are as defined herein.

[00169] In some embodiments, an ASBTI suitable for the methods described herein is a compound of Formula I:

[00170]



Formula I

[00171] wherein:

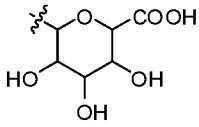
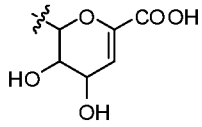
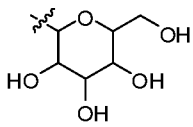
[00172] R^1 is a straight chained C_{1-6} alkyl group;

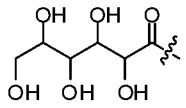
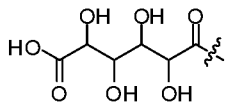
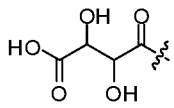
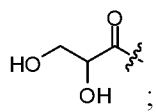
[00173] R^2 is a straight chained C_{1-6} alkyl group;

[00174] R^3 is hydrogen or a group OR^{11} in which R^{11} is hydrogen, optionally substituted C_{1-6} alkyl or a C_{1-6} alkylcarbonyl group;

[00175] R^4 is pyridyl or optionally substituted phenyl or $-L_z$-K_z; wherein z is 1, 2 or 3; each L is independently a substituted or unsubstituted alkyl, a substituted or unsubstituted heteroalkyl, a substituted or unsubstituted alkoxy, a substituted or unsubstituted aminoalkyl group, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted cycloalkyl, or a substituted or unsubstituted heterocycloalkyl; each K is a moiety that prevents systemic absorption;

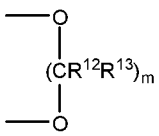
[00176] R^5, R^6, R^7 and R^8 are the same or different and each is selected from hydrogen, halogen, cyano, R^5-acetylide, OR^{15}, optionally substituted C_{1-6} alkyl, COR^{15}, $CH(OH)R^{15}$, $S(O)_nR^{15}$, $P(O)(OR^{15})_2$, $OCOR^{15}$, OCF3, OCN, SCN, NHCN, CH_2OR^{15}, CHO, $(CH_2)_pCN$, $CONR^{12}R^{13}$, $(CH_2)_pCO_2R^{15}$, $(CH_2)_pNR^{12}R^{13}$, CO_2R^{15}, $NHCOCF_3$, $NHSO_2R^{15}$, OCH_2OR^{15}, $OCH{=}CHR^{15}$, $O(CH_2CH_2O)_nR^{15}$, $O(CH_2)_pSO_3R^{15}$, $O(CH_2)_pNR^{12}R^{13}$, $O(CH_2)_pN^+R^{12}R^{13}R^{14}$ and–W-R^{31}, wherein W is O or NH and R^{31} is selected from


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,

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[00177]

,

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and

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[00178] wherein p is an integer from 1–4, n is an integer from 0–3 and, R^{12}, R^{13}, R^{14} and R^{15} are independently selected from hydrogen and optionally substituted C_{1-6} alkyl; or

[00179] R^6 and R^7 are linked to form a group

[00180]


[00181] wherein R^{12} and R^{13} are as hereinbefore defined and m is 1 or 2; and

[00182] R^9 and R^{10} are the same or different and each is selected from hydrogen or C_{1-6} alkyl; and

[00183] salts, solvates and physiologically functional derivatives thereof.

[00184] In some embodiments of the methods, the compound of Formula I is a compound

[00185] wherein

[00186] R^1 is a straight chained C_{1-6} alkyl group;

[00187] R^2 is a straight chained C_{1-6} alkyl group;

[00188] R^3 is hydrogen or a group OR^{11} in which R^{11} is hydrogen, optionally substituted C_{1-6} alkyl or a C_{1-6} alkylcarbonyl group;

[00189] R^4 is optionally substituted phenyl;

[00190] R^5, R^6 and R^8 are independently selected from hydrogen, C_{1-4} alkyl optionally substituted by fluorine, C_{1-4} alkoxy, halogen, or hydroxy;

[00191] R^7 is selected from halogen, cyano, R^{15}-acetylide, OR^{15}, optionally substituted C_{1-6} alkyl, COR^{15}, $CH(OH)R^{15}$, $S(O)_nR^{15}$, $P(O)(OR^{15})_2$, $OCOR^{15}$, OCF_3, OCN, SCN, HNCN, CH_2OR^{15}, CHO, $(CH_2)_pCN$, $CONR^{12}R^{13}$, $(CH_2)_pCO_2R^{15}$, $(CH_2)_pNR^{12}R^{13}$, CO_2R^{15}, $NHCOCF_3$, $NHSO_2R^{15}$, OCH_2OR^{15}, $OCH{=}CHR^{15}$, $O(CH_2CH_2O)_pR^{15}$, $O(CH_2)_pSO_3R^{15}$, $O(CH_2)_pNR^{12}R^{13}$ and $O(CH_2)_pN^+R^{12}R^{13}R^{14}$;

[00192] wherein n, p and R^{12} to R^{15} are as hereinbefore defined;

[00193] with the proviso that at least two of R^5 to R^8 are not hydrogen; and

[00194] salts solvates and physiologically functional derivatives thereof.

[00195] In some embodiments of the methods described herein, the compound of Formula I is a compound

[00196] wherein

[00197] R^1 is a straight chained C_{1-6} alkyl group;

[00198] R^2 is a straight chained C_{1-6} alkyl group;

[00199] R^3 is hydrogen or a group OR^{11} in which R^{11} is hydrogen, optionally substituted C_{1-6} alkyl or a C_{1-6} alkylcarbonyl group;

[00200] R^4 is un-substituted phenyl;

[00201] R^5 is hydrogen or halogen;

[00202] R^6 and R^8 are independently selected from hydrogen, C_{1-4} alkyl optionally substituted by fluorine, C_{1-4} alkoxy, halogen, or hydroxy;

[00203] R^7 is selected from OR^{15}, $S(O)_nR^{15}$, $OCOR^{15}$, OCF_3, OCN, SCN, CHO, OCH_2OR^{15}, $OCH{=}CHR^{15}$, $O(CH_2CH_2O)nR^{15}$, $O(CH_2)_pSO_3R^{15}$, $O(CH_2)_pNR^{12}R^{13}$ and $O(CH_2)_pN^+R^{12}R^{13}R^{14}$ wherein p is an integer from 1–4, n is an integer from 0–3, and R^{12}, R^{13}, R^{14}, and R^{15} are independently selected from hydrogen and optionally substituted C_{1-6} alkyl;

[00204] R^9 and R^{10} are the same or different and each is selected from hydrogen or C_{1-6} alkyl; and

[00205] salts, solvates and physiologically functional derivatives thereof.

[00206] In some embodiments of the methods, wherein the compound of Formula I is a compound

[00207] wherein

[00208] R^1 is methyl, ethyl or n-propyl;

[00209] R^2 is methyl, ethyl, n-propyl, n-butyl or n-pentyl;

[00210] R^3 is hydrogen or a group OR^{11} in which R^{11} is hydrogen, optionally substituted C_{1-6} alkyl or a C_{1-6} alkylcarbonyl group;

[00211] R^4 is un-substituted phenyl;

[00212] R^5 is hydrogen;

[00213] R^6 and R^8 are independently selected from hydrogen, C_{1-4} alkyl optionally substituted by fluorine, C_{1-4} alkoxy, halogen, or hydroxy;

[00214] R^7 is selected from OR^{15}, $S(O)_nR^{15}$, $OCOR^{15}$, OCF_3, OCN, SCN, CHO, OCH_2OR^{15}, $OCH{=}CHR^{15}$, $O(CH_2CH_2O)nR^{15}$, $O(CH_2)_pSO_3R^{15}$, $O(CH_2)_pNR^{12}R^{13}$ and $O(CH_2)_pN^+R^{12}R^{13}R^{14}$ wherein p is an integer from 1–4, n is an integer from 0–3, and R^{12}, R^{13}, R^{14}, and R^{15} are independently selected from hydrogen and optionally substituted C_{1-6} alkyl;

[00215] R^9 and R^{10} are the same or different and each is selected from hydrogen or C_{1-6} alkyl; and salts, solvates and physiologically functional derivatives thereof.

[00216] In some embodiments of the methods, the compound of Formula I is a compound

[00217] wherein

[00218] R^1 is methyl, ethyl or n-propyl;

[00219] R^2 is methyl, ethyl, n-propyl, n-butyl or n-pentyl;

[00220] R^3 is hydrogen or a group OR^{11} in which R^{11} is hydrogen, optionally substituted C_{1-6} alkyl or a C_{1-6} alkylcarbonyl group;

[00221] R^4 is un-substituted phenyl;

[00222] R^5 is hydrogen;

[00223] R^6 is C_{1-4} alkoxy, halogen, or hydroxy;

[00224] R^7 is OR^{15}, wherein R^{15} is hydrogen or optionally substituted C_{1-6} alkyl;

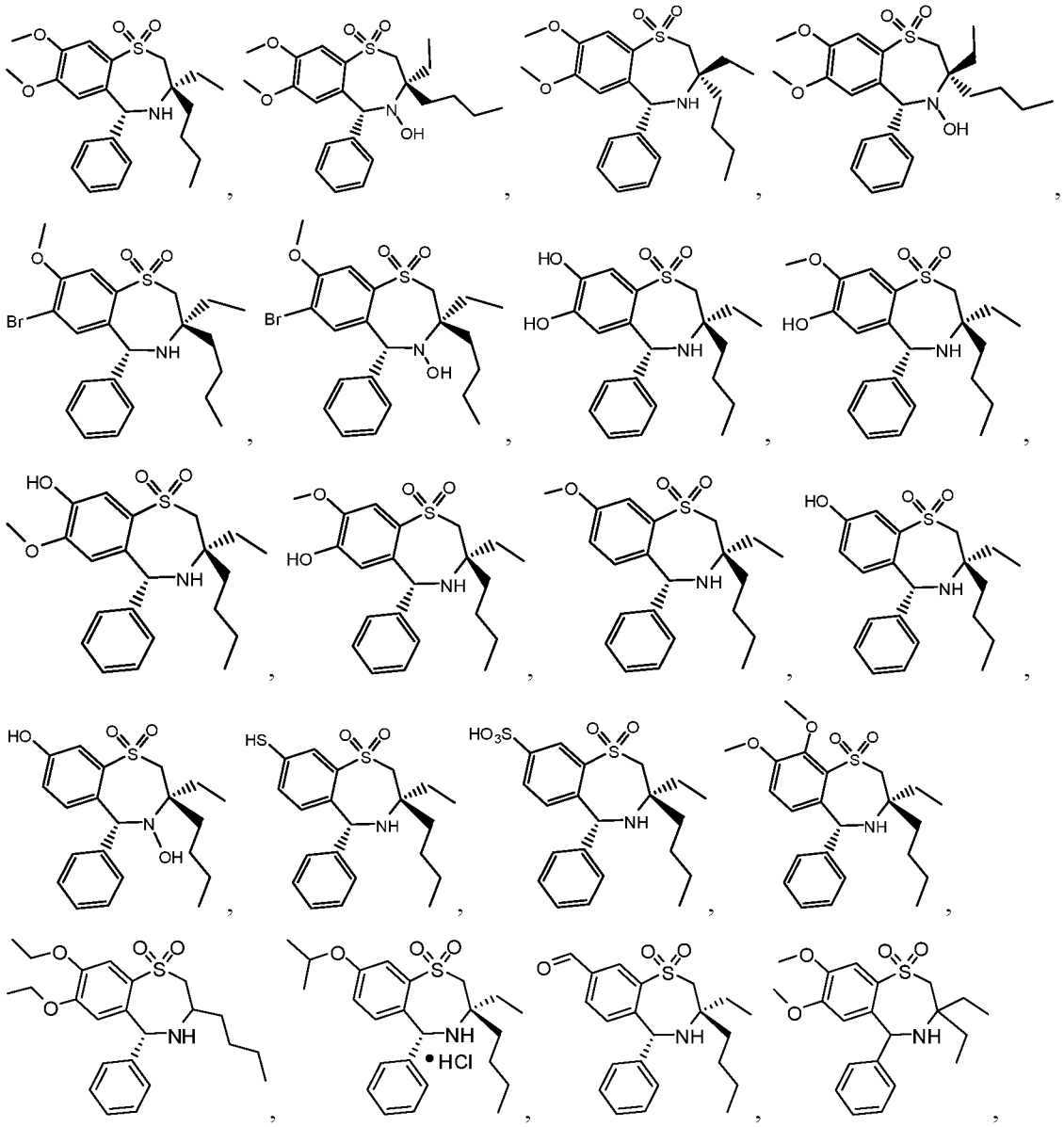
[00225] R^8 is hydrogen or halogen;

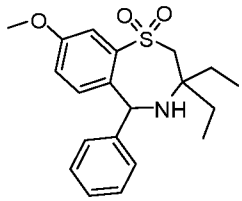
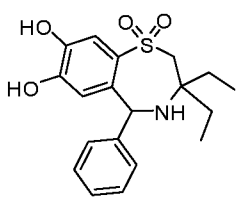
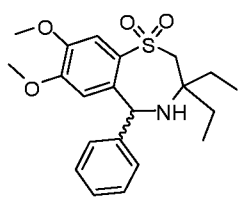
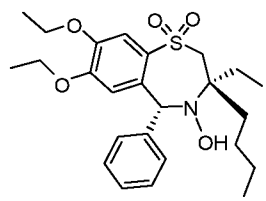
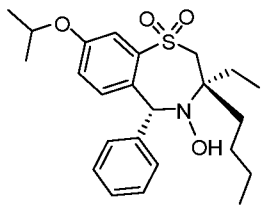
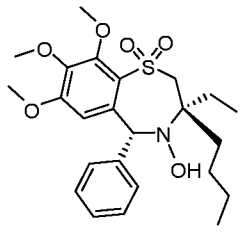
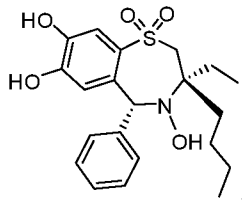
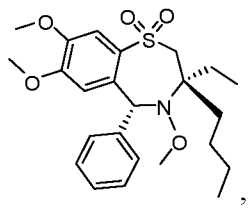
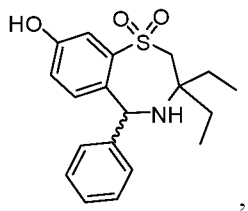
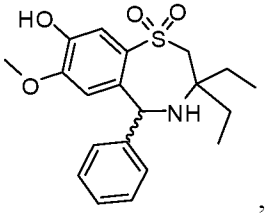
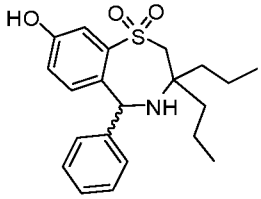
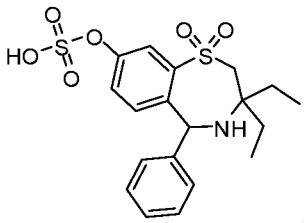
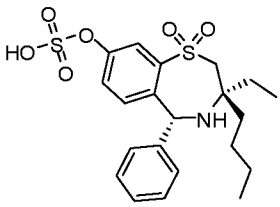
[00226] R^9 and R^{10} are the same or different and each is selected from hydrogen or C_{1-6} alkyl; and salts, solvates and physiologically functional derivatives thereof.

[00227] In some embodiments of the methods, the compound of Formula I is (3R,5R)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7,8- dimethoxy-5-phenyl-1,4-benzothiazepine 1,1-dioxide; (3R,5R)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7,8- dimethoxy-5-phenyl-1,4-benzothiazepin-4-ol 1,1-dioxide; (±)-Trans-3-butyl-3-ethyl-2,3,4,5-tetrahydro-7,8-dimethoxy-5-phenyl-1,4-benzothiazepine 1,1-dioxide; (±)-Trans-3-butyl-3-ethyl-2,3,4,5-tetrahydro-7,8- dimethoxy-5-phenyl-1,4,-benzothiazepin-4-ol 1,1-dioxide; (3R,5R)-7-Bromo-3-butyl-3-ethyl-2,3,4,5-tetrahydro-8-methoxy-5-phenyl-1,4-benzothiazepine 1,1-dioxide; (3R,5R)-7-Bromo-3-butyl-3-ethyl-2,3,4,5-tetrahydro-8-methoxy-5-phenyl-1,4-benxothiaxepin-4-ol 1,1 - dioxide; (3R,5R)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1, 4-benzothiazepine-7,8-diol 1,1-dioxide; (3R,5R)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-8-methoxy- 5-phenyl-1,4-benzothiazepin-7-ol 1,1-dioxide; (3R,5R)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7-methoxy- 5-phenyl-1,4-benzothiazepin-8-ol 1,1-dioxide; (±)-Trans-3-butyl-3-ethyl-2,3,4,5-tetrahydro-8-methoxy-5-phenyl-1,4-benzothiazepine 1,1-dioxide; (±)-Trans-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl- 1,4-benzothiazepin-8-ol 1,1-dioxide; (±)-Trans-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine-4,8-diol; (±)-Trans-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepin-8-thiol 1,1-dioxide; (±)-Trans-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepin-8-sulfonic acid 1,1-dioxide; (±)-Trans-3-butyl-3-ethyl-2,3,4,5-tetrahydro-8,9-dimethoxy-5-phenyl-1,4-benzothiazepine 1, 1-dioxide; (3R,5R)-3-butyl-7,8-diethoxy-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide; (±)-Trans-3-butyl-8-ethoxy-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide; (±)-Trans-3-butyl-3-ethyl-2,3,4,5-tetrahydro-8-isopropoxy-5-phenyl-1,4-benzothiazepine 1,1-dioxide hydrochloride; (±)-Trans-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepin-8-carbaldehyde-1,1-dioxide; 3,3-Diethyl-2,3,4,5-tetrahydro-7,8-dimethoxy-5-phenyl-1,4-benzothiazepine 1,1-dioxide; 3,3-Diethyl-2,3,4,5-tetrahydro-8-methoxy-5-phenyl-1,4-benzothiazepine 1,1-dioxide; 3,3-Diethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazpin-4,8-diol 1,1-dioxide; (RS)-3,3-Diethyl-2,3 ,4,5-tetrahydro-4-hydroxy-7,8-dimethoxy-5-phenyl-1,4-benzothiazepine 1,1-dioxide; (±)-Trans-3-butyl-8-ethoxy-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepin-4-ol-1-dioxide; (±)-Trans-3-butyl-3-ethyl-2,3,4,5-tetrahydro-8-isopropoxy-5-phenyl-1,4-benzothiazepin-4-ol 1,1-dioxide; (±)-Trans-3-butyl-3-ethyl-2,3,4,5-tetrahydro-7,8,9-trimethoxy-5-phenyl-1,4-benzothiazepin-4-ol 1,1-dioxide; (3R,5R)-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepin-4,7,8-triol 1,1-dioxide; (±)-Trans-3-butyl-3-ethyl-2,3,4,5-tetrahydro-4,7,8-trimethoxy-5-phenyl-1,4-benzothiazepine 1,1-dioxide; 3,3- Diethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepin-8-

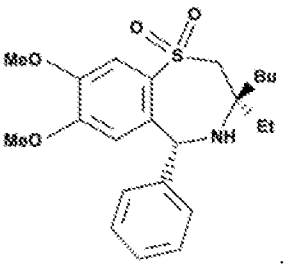
ol 1,1-dioxide; 3,3-Diethyl-2,3,4,5-tetrahydro-7-methoxy-5-phenyl-1,4-benzothiazepin-8-ol 1,1-dioxide; 3,3Dibutyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepin-8-ol 1,1-dioxide; (±)-Trans-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-1,1-dioxo-5-phenyl-1,4-benzothiazepin-8-yl hydrogen sulfate; or 3,3-Diethyl-2,3,4,5-tetrahydro-1,1-dioxo-5-phenyl-1,4-benzothiazepin-8-yl hydrogen sulfate.

[00228] In some embodiments, the compound of Formula I is

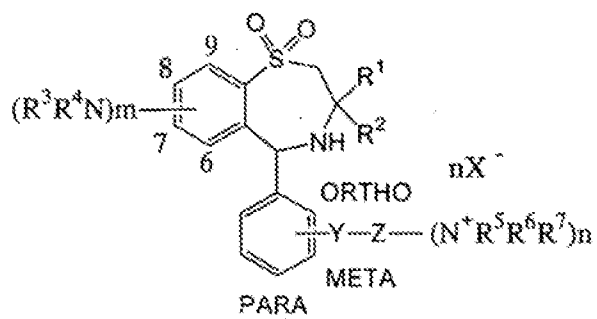



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or .

[00229] In some embodiments of the methods, the compound of Formula I is

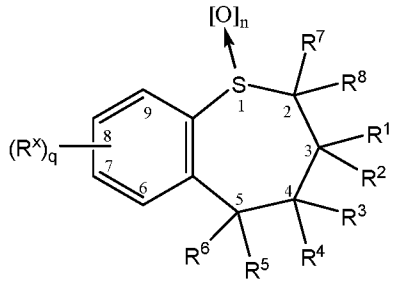

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[00230] In some embodiments, the compound of Formula I is not a structure shown as:



[00231] wherein m represents an integer of 1 or 2, and R^3 and R^4, which may be mutually different, each represents an alkyl group having 1 to 5 carbon atoms.

[00232] In some embodiments, an ASBTI suitable for the methods described herein is a compound of Formula II



Formula II

[00233] wherein:

[00234] q is an integer from 1 to 4;

[00235] n is an integer from 0 to 2;

[00236] R^1 and R^2 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

[00237] wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituents selected from the group consisting of OR^9, NR^9R^{10}, $N^+R^9R^{10}R^wA^-$, SR^9, $S^+R^9R^{10}A^-$, $P^+R^9R^{10}R^{11}A^-$, $S(O)R^9$, SO_2R^9, SO_3R^9, CO_2R^9, CN, halogen, oxo, and $CONR^9R^{10}$,

[00238] wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally have one or more carbons replaced by O, NR^9, $N^+R^9R^{10}A^-$, S, SO, SO_2, $S^+R^9A^-$, $P^+R^9R^{10}$ A^-, or phenylene,

[00239] wherein R^9, R^{10}, and R^w are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, and alkylammoniumalkyl; or

[00240] R^1 and R^2 taken together with the carbon to which they are attached form C_3-C_{10} cycloalkyl;

[00241] R^3 and R^4 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocycle, OR^9, NR^9R^{10}, SR^9, $S(O)R^9$, SO_2R^9, and SO_3R^9, wherein R^9 and R^{10} are as defined above; or

[00242] R^3 and R^4 together =O, $=NOR^{11}$, =S, $=NNR^{11}R^{12}$, $=NR^9$, or $=CR^{11}R^{12}$,

[00243] wherein R^{11} and R^{12} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, OR^9, NR^9R^{10}, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, CO_2R^9, CN, halogen, oxo, and $CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above, provided that both R^3 and R^4 cannot be OH, NH_2, and SH, or

[00244] R^{11} and R^{12} together with the nitrogen or carbon atom to which they are attached form a cyclic ring;

[00245] R^5 and R^6 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, quarternary heteroaryl, OR^9, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, and $-L_z$-K_z;

[00246] wherein z is 1, 2 or 3; each L is independently a substituted or unsubstituted alkyl, a substituted or unsubstituted heteroalkyl, a substituted or unsubstituted alkoxy, a substituted or unsubstituted aminoalkyl group, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted cycloalkyl, or a substituted or unsubstituted heterocycloalkyl; each K is a moiety that prevents systemic absorption;

[00247] wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, and quaternary heteroaryl can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, halogen, oxo, R^{15}, OR^{13}, $OR^{13}R^{14}$, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, SO_3R^{13}, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, C(O)OM, CR^{13}, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$,

[00248] wherein:

[00249] A^- is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation, said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7, NR^7R^8, $S(O)R^7$, SO_2R^7, SO_3R^7, CO_2R^7, CN, oxo, $CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8R^9A^-$, and $P(O)(OR^7)$ OR^8 and

[00250] wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR^7, $N^+R^7R^8A^-$, S, SO, SO_2, $S^+R^7A^-$, PR^7, $P(O)R^7$, $P^+R^7R^8A^-$, or phenylene, and R^{13}, R^{14}, and R^{15}

are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, aryl, arylalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heteroaryl, quaternary heteroarylalkyl, and –G-T-V-W,

[00251] wherein alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl optionally have one or more carbons replaced by O, NR^9, $N^+R^9R^{10}A^-$, S, SO, SO_2, $S^+R^9A^-$, PR, $P^+R^9R^{10}A^-$, $P(O)R^9$, phenylene, carbohydrate, C_2-C_7 polyol, amino acid, peptide, or polypeptide, and

[00252] G, T and V are each independently a bond, -O-, -S-, -N(H)-, substituted or unsubstituted alkyl, -O-alkyl, -N(H)-alkyl, -C(O)N(H)-, -N(H)C(O)-, -N(H)C(O)N(H)-, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted alkenylalkyl, alkynylalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heterocycle, substituted or unsubstituted carboxyalkyl, substituted or unsubstituted carboalkoxyalkyl, or substituted or unsubstituted cycloalkyl, and

[00253] W is quaternary heterocycle, quaternary heteroaryl, quaternary heteroarylalkyl, $N^+R^9R^{11}R^{12}A^-$, $P^+R^9R^{10}R^{11}A^-$, $OS(O)_2OM$, or $S^+R^9R^{10}A^-$, and

[00254] R^{13}, R^{14} and R^{15} are optionally substituted with one or more groups selected from the group consisting of sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, OR^9, NR^9R^{10}, $N^+R^9R^{11}R^{12}A^-$, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, oxo, CO_2R^9, CN, halogen, $CONR^9R^{10}$, SO_2OM, $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, $P^+R^9R^{10}R^{11}A^-$, $S^+R^9R^{10}A^-$, and C(O)OM,

[00255] wherein R^{16} and R^{17} are independently selected from the substituents constituting R^9 and M; or

[00256] R^{14} and R^{15}, together with the nitrogen atom to which they are attached, form a cyclic ring; and

[00257] is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, and arylalkyl; and

[00258] R^7 and R^8 are independently selected from the group consisting of hydrogen and alkyl; and

[00259] one or more R^x are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle, heteroaryl, polyether, quaternary heterocycle, quaternary heteroaryl, OR^{13}, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, $S(O)_2R^{13}$, SO_3R^{13}, $S^+R^{13}R^{14}A^-$, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$, $C(O)NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$,

C(O)OM, COR^{13}, OR^{18}, $S(O)_n NR^{18}$, $NR^{13}R^{18}$, $NR^{18}R^{14}$, $N^+R^9R^{11}R^{12}A^-$, $P^+R^9R^{11}R^{12}A^-$, amino acid, peptide, polypeptide, and carbohydrate,

[00260] wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and quaternary heteroaryl can be further substituted with OR^9, NR^9R^{10}, $N^+R^9R^{11}R^{12}A^-$, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, oxo, CO_2R^9, CN, halogen, $CONR^9R^{10}$, SO_2OM, $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, $P^+R^9R^{11}R^{12}A^-$, $S^+R^9R^{10}A^-$, or C(O)M, and

[00261] wherein R^{18} is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl,

[00262] wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, quaternary heterocycle, and quaternary heteroaryl optionally are substituted with one or more substituents selected from the group consisting of OR^9, NR^9R^{10}, $N^+R^9R^{11}R^{12}A^-$, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, oxo, CO_3R^9, CN, halogen, $CONR^9R^{10}$, SO_3R^9, SO_2OM, $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, and C(O)OM,

[00263] wherein in R^x, one or more carbons are optionally replaced by O, NR^{13}, $N^+R^{13}R^{14}A^-$, S, SO, SO_2, $S^+R^{13}A^-$, PR^{13}, $P(O)R^{13}$, $P^+R^{13}R^{14}A^-$, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl,

[00264] wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR^9, $R^9R^{10}A^-$, S, SO, SO_2, $S^+R^9A^-$, PR^9, $P^+R^9R^{10}A^-$, or $P(O)R^9$;

[00265] wherein quaternary heterocycle and quaternary heteroaryl are optionally substituted with one or more groups selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13}, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, SO_3R^{13}, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, C(O)OM, COR^{13}, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$,

[00266] provided that both R^5 and R^6 cannot be hydrogen or SH;

[00267] provided that when R^5 or R^6 is phenyl, only one of R^1 or R^2 is H;

[00268] provided that when q=1 and R^x is styryl, anilido, or anilinocarbonyl, only one of R^5 or R^6 is alkyl; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00269] In some embodiments of the methods, the compound of Formula II is a compound wherein

[00270] q is an integer from 1 to 4;

[00271] n is 2;

[00272] R^1 and R^2 are independently selected from the group consisting of H, alkyl, alkoxy, dialkylamino, and alkylthio,

[00273] wherein alkyl, alkoxy, dialkylamino, and alkylthio are optionally substituted with one or more substituents selected from the group consisting of OR^9, NR^9R^{10}, SR^9, SO_2R^9, CO_2R^9, CN, halogen, oxo, and $CONR^9R^{10}$;

[00274] each R^9 and R^{10} are each independently selected from the group consisting of H, alkyl, cycloalkyl, aryl, acyl, heterocycle, and arylalkyl;

[00275] R^3 and R^4 are independently selected from the group consisting of H, alkyl, acyloxy, OR^9, NR^9R^{10}, SR^9, and SO_2R^9, wherein R^9 and R^{10} are as defined above;

[00276] R^{11} and R^{12} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, OR^9, NR^9R^{10}, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, CO_2R^9, CN, halogen, oxo, and $CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above, provided that both R^3 and R^4 cannot be OH, NH_2, and SH, or

[00277] R^{11} and R^{12} together with the nitrogen or carbon atom to which they are attached form a cyclic ring;

[00278] R^5 and R^6 are independently selected from the group consisting of H, alkyl, aryl, cycloalkyl, heterocycle, and $–L_z\text{-}K_z$;

[00279] wherein z is 1 or 2; each L is independently a substituted or unsubstituted alkyl, a substituted or unsubstituted heteroalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted cycloalkyl, or a substituted or unsubstituted heterocycloalkyl; each K is a moiety that prevents systemic absorption;

[00280] wherein alkyl, aryl, cycloalkyl, and heterocycle can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, halogen, oxo, OR^{13}, $OR^{13}R^{14}$, $NR^{13}R^{14}$, SR^{13}, SO_2R^{13}, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, and CR^{13},

[00281] wherein:

[00282] A^- is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation;

[00283] R^{13}, R^{14}, and R^{15} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, aryl, arylalkyl, cycloalkyl, heterocycle, heteroaryl,

quaternary heterocycle, quaternary heteroaryl, and quaternary heteroarylalkyl, wherein R^{13}, R^{14} and R^{15} are optionally substituted with one or more groups selected from the group consisting of quaternary heterocycle, quaternary heteroaryl, OR^9, NR^9R^{10}, $N^+R^9R^{11}R^{12}A^-$, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, oxo, CO_2R^9, CN, halogen, and $CONR^9R^{10}$; or

[00284] R^{14} and R^{15}, together with the nitrogen atom to which they are attached, form a cyclic ring; and

[00285] is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, and arylalkyl; and

[00286] R^7 and R^8 are independently selected from the group consisting of hydrogen and alkyl; and

[00287] one or more R^x are independently selected from the group consisting of H, alkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle, heteroaryl, OR^{13}, $NR^{13}R^{14}$, SR^{13}, $S(O)_2R^{13}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, $SO_2NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$, $C(O)NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$, and COR^{13};

[00288] provided that both R^5 and R^6 cannot be hydrogen;

[00289] provided that when R^5 or R^6 is phenyl, only one of R^1 or R^2 is H;

[00290] provided that when q=1 and R^x is styryl, anilido, or anilinocarbonyl, only one of R^5 or R^6 is alkyl; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00291] In some embodiments, the compound of Formula II is a compound wherein

[00292] q is 1;

[00293] n is 2;

[00294] R^x is $N(CH_3)_2$;

[00295] R^7 and R^8 are independently H;

[00296] R^1 and R^2 is alkyl;

[00297] R^3 is H, and R^4 is OH;

[00298] R^5 is H, and R^6 is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, quarternary heteroaryl, OR^9, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, and $-L_z$-K_z;

[00299] wherein z is 1, 2 or 3; each L is independently a substituted or unsubstituted alkyl, a substituted or unsubstituted heteroalkyl, a substituted or unsubstituted alkoxy, a substituted or unsubstituted aminoalkyl group, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted cycloalkyl, or a substituted or unsubstituted heterocycloalkyl; each K is a moiety that prevents systemic absorption;

[00300] wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, and quaternary heteroaryl can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, halogen, oxo, R^{15}, OR^{13}, $OR^{13}R^{14}$, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, SO_3R^{13}, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, C(O)OM, CR^{13}, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$,

[00301] wherein A^- is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation, said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7, NR^7R^8, $S(O)R^7$, SO_2R^7, SO_3R^7, CO_2R^7, CN, oxo, $CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8R^9A^-$, and $P(O)(OR^7)\ OR^8$ and

[00302] wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR^7, $N^+R^7R^8A^-$, S, SO, SO_2, $S^+R^7A^-$, PR^7, $P(O)R^7$, $P^+R^7R^8A^-$, or phenylene, and R^{13}, R^{14}, and R^{15} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, aryl, arylalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heteroaryl, quaternary heteroarylalkyl, and –G-T-V-W,

[00303] wherein alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl optionally have one or more carbons replaced by O, NR^9, $N^+R^9R^{10}A^-$, S, SO, SO_2, $S^+R^9A^-$, PR, $P^+R^9R^{10}A^-$, $P(O)R^9$, phenylene, carbohydrate, C_2-C_7 polyol, amino acid, peptide, or polypeptide, and

[00304] G, T and V are each independently a bond, -O-, -S-, -N(H)-, substituted or unsubstituted alkyl, -O-alkyl, -N(H)-alkyl, -C(O)N(H)-, -N(H)C(O)-, -N(H)C(O)N(H)-, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted alkenylalkyl, alkynylalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heterocycle, substituted or unsubstituted carboxyalkyl, substituted or unsubstituted carboalkoxyalkyl, or substituted or unsubstituted cycloalkyl, and

[00305] W is quaternary heterocycle, quaternary heteroaryl, quaternary heteroarylalkyl, $N^+R^9R^{11}R^{12}A^-$, $P^+R^9R^{10}R^{11}A^-$, $OS(O)_2OM$, or $S^+R^9R^{10}A^-$, and

[00306] R^9 and R^{10} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, and alkylammoniumalkyl;

[00307] R^{11} and R^{12} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, OR^9, NR^9R^{10}, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, CO_2R^9, CN, halogen, oxo, and $CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above, provided that both R^3 and R^4 cannot be OH, NH_2, and SH, or

[00308] R^{11} and R^{12} together with the nitrogen or carbon atom to which they are attached form a cyclic ring;

[00309] R^{13}, R^{14} and R^{15} are optionally substituted with one or more groups selected from the group consisting of sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, OR^9, NR^9R^{10}, $N^+R^9R^{11}R^{12}A^-$, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, oxo, CO_2R^9, CN, halogen, $CONR^9R^{10}$, SO_2OM, $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, $P^+R^9R^{10}R^{11}A^-$, $S^+R^9R^{10}A^-$, and C(O)OM,

[00310] wherein R^{16} and R^{17} are independently selected from the substituents constituting R^9 and M; or

[00311] R^{14} and R^{15}, together with the nitrogen atom to which they are attached, form a cyclic ring; and is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, and arylalkyl;

[00312] or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00313] In some embodiments, the compound of Formula II is a compound wherein

[00314] q is 1;

[00315] n is 2;

[00316] R^x is $N(CH_3)_2$;

[00317] R^7 and R^8 are independently H;

[00318] R^1 and R^2 is independently C_1-C_4 alkyl;

[00319] R^3 is H, and R^4 is OH;

[00320] R^5 is H, and R^6 is arylsubstituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, halogen, oxo, R^{15}, OR^{13}, $OR^{13}R^{14}$, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, SO_3R^{13}, $NR^{13}OR^{14}$,

$NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, C(O)OM, CR^{13}, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$,

[00321] wherein A^- is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation, said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7, NR^7R^8, $S(O)R^7$, SO_2R^7, SO_3R^7, CO_2R^7, CN, oxo, $CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8R^9A^-$, and $P(O)(OR^7)\ OR^8$ and

[00322] wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR^7, $N^+R^7R^8A^-$, S, SO, SO_2, $S^+R^7A^-$, PR^7, $P(O)R^7$, $P^+R^7R^8A^-$, or phenylene, and R^{13}, R^{14}, and R^{15} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, aryl, arylalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heteroaryl, quaternary heteroarylalkyl, and –G-T-V-W,

[00323] wherein alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl optionally have one or more carbons replaced by O, NR^9, $N^+R^9R^{10}A^-$, S, SO, SO_2, $S^+R^9A^-$, PR, $P^+R^9R^{10}A^-$, $P(O)R^9$, phenylene, carbohydrate, C_2-C_7 polyol, amino acid, peptide, or polypeptide, and

[00324] G, T and V are each independently a bond, -O-, -S-, -N(H)-, substituted or unsubstituted alkyl, -O-alkyl, -N(H)-alkyl, -C(O)N(H)-, -N(H)C(O)-, -N(H)C(O)N(H)-, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted alkenylalkyl, alkynylalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heterocycle, substituted or unsubstituted carboxyalkyl, substituted or unsubstituted carboalkoxyalkyl, or substituted or unsubstituted cycloalkyl, and

[00325] W is quaternary heterocycle, quaternary heteroaryl, quaternary heteroarylalkyl, $N^+R^9R^{11}R^{12}A^-$, $P^+R^9R^{10}R^{11}A^-$, $OS(O)_2OM$, or $S^+R^9R^{10}A^-$, and

[00326] R^9 and R^{10} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, and alkylammoniumalkyl;

[00327] R^{11} and R^{12} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl,

carboalkoxyalkyl, cycloalkyl, cyanoalkyl, OR^9, NR^9R^{10}, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, CO_2R^9, CN, halogen, oxo, and $CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above, provided that both R^3 and R^4 cannot be OH, NH_2, and SH, or

[00328] R^{11} and R^{12} together with the nitrogen or carbon atom to which they are attached form a cyclic ring;

[00329] R^{13}, R^{14} and R^{15} are optionally substituted with one or more groups selected from the group consisting of sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, OR^9, NR^9R^{10}, $N^+R^9R^{11}R^{12}A^-$, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, oxo, CO_2R^9, CN, halogen, $CONR^9R^{10}$, SO_2OM, $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, $P^+R^9R^{10}R^{11}A^-$, $S^+R^9R^{10}A^-$, and C(O)OM,

[00330] wherein R^{16} and R^{17} are independently selected from the substituents constituting R^9 and M; or

[00331] R^{14} and R^{15}, together with the nitrogen atom to which they are attached, form a cyclic ring; and is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, and arylalkyl;

[00332] or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00333] In some embodiments of the methods, the compound of Formula II is a compound

[00334] wherein

[00335] R^5 and R^6 are independently selected from the group consisting of H, aryl, heterocycle, quaternary heterocycle, and quarternary heteroaryl

[00336] wherein the aryl, heteroaryl, quaternary heterocycle and quaternary heteroaryl are optionally substituted with one or more groups selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13}, $OR^{13}R^{14}$, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, SO_3R^{13}, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, C(O)OM, COR^{13}, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, $N^+R^9R^{11}R^{12}A^-$ and $-L_z\text{-}K_z$.

[00337] In some embodiments of the methods, the compound of Formula II is a compound

[00338] wherein

[00339] R^5 or R^6 is $-Ar\text{-}(R^y)_t$

[00340] t is an integer from 0 to 5;

[00341] Ar is selected from the group consisting of phenyl, thiophenyl, pyridyl, piperazinyl, piperonyl, pyrrolyl, naphthyl, furanyl, anthracenyl, quinolinyl, isoquinolinyl, quinoxalinyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, pyrimidinyl, thiazolyl, triazolyl, isothiazolyl, indolyl, benzoimidazolyl, benzoxazolyl, benzothiazolyl, and benzoisothiazolyl; and

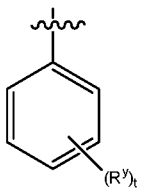
[00342] one or more R^y are independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, halo alkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13}, $OR^{13}R^{14}$, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, SO_3R^{13}, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, C(O)OM, COR^{13}, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, $N^+R^9R^{11}R^{12}A^-$ and $-L_z\text{-}K_z$;

[00343] wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^{13}, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, SO_3R^{13}, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, oxo, $CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8A^-$, and $P(O)(OR^7)OR^8$, and or phenylene;

[00344] wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR^7, $N^+R^7R^8A^-$, S, SO, SO_2, $S^+R^7A^-$, PR^7, $P(O)R^7$, $P^+R^7R^8A^-$, or phenylene.

[00345] In some embodiments of the methods, the compound of Formula II is a compound wherein

[00346] R^5 or R^6 is

[00347] 

[00348] In some embodiments of the methods, the compound of Formula II is a compound wherein n is 1 or 2. In some embodiments of the methods, the compound of Formula II is a compound wherein R^1 and R^2 are independently H or $C_{1\text{-}7}$ alkyl. In some embodiments of the methods, the compound of Formula II is a compound wherein each $C_{1\text{-}7}$ alkyl is independently ethyl, n-propyl, n-butyl, or isobutyl. In some embodiments of the methods, the compound of Formula II is a compound wherein R^3 and R^4 are independently H or OR^9. In some embodiments of the methods, compound of Formula II is a compound wherein R^9 is H

[00349] In some embodiments of the methods, the compound of Formula II is a compound wherein one or more R^x are in the 7-, 8- or 9- position of the benzo ring of Formula II. In some embodiments of the methods, the compound of Formula II is a compound wherein R^x is in the 7- position of the benzo ring of Formula II. In some embodiments of the methods, the

compound of Formula II is a compound wherein one or more R^x are independently selected from OR^{13} and $NR^{13}R^{14}$.

[00350] In some embodiments of the methods, the compound of Formula II is a compound

[00351] wherein:

[00352] q is 1 or 2;

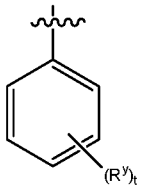
[00353] n is 2;

[00354] R^1 and R^2 are each alkyl;

[00355] R^3 is hydroxy;

[00356] R^4 and R^6 are hydrogen;

[00357] R^5 has the formula

[00358] 

[00359] wherein

[00360] t is an integer from 0 to 5;

[00361] one or more R^Y are OR^{13} or $OR^{13}R^{14}$;

[00362] R^{13} and R^{14} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, aryl, arylalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heteroaryl, and quaternary heteroarylalkyl;

[00363] wherein said alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl groups optionally have one or more carbons replaced by O, NR^9, $N^+R^9R^{10}A^-$, S, SO, SO_2, $S^+R^9A^-$, PR^9, $P^+R^9R^{10}A^-$, $P(O)R^9$, phenylene, carbohydrate, amino acid, peptide, or polypeptide;

[00364] R^{13} and R^{14} are optionally substituted with one or more groups independently selected from the group consisting of sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, OR^9, NR^9R^{10}, $N^+R^9R^{11}R^{12}A^-$, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, oxo, CO_2R^9, CN, halogen, $CONR^9R^{10}$, SO_2OM, $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, $P^+R^9R^{10}R^{11}A^-$, $S^+R^9R^{10}A^-$, and C(O)OM,

[00365] wherein A is a pharmaceutically acceptable anion, and M is a pharmaceutically acceptable cation,

[00366] R^9 and R^{10} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, and alkylammoniumalkyl;

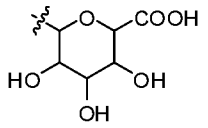
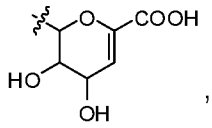
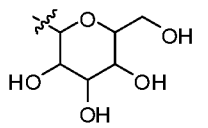
[00367] R^{11} and R^{12} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, OR^9, NR^9R^{10}, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, CO_2R^9, CN, halogen, oxo, and $CONR^9R^{10}$, wherein R^9 and $R^{1°}$ are as defined above, provided that both R^3 and R^4 cannot be OH, NH_2, and SH; or

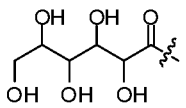
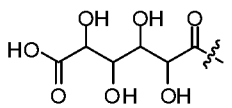
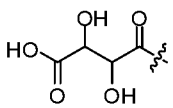
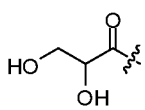
[00368] R^{11} and R^{12} together with the nitrogen or carbon atom to which they are attached form a cyclic ring; and

[00369] R^{16} and R^{17} are independently selected from the substituents constituting R^9 and M;

[00370] R^7 and R^8 are hydrogen; and

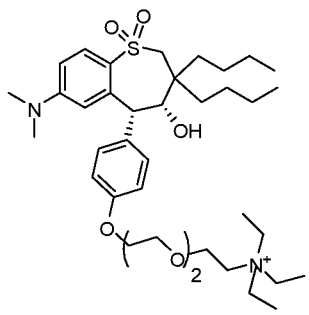
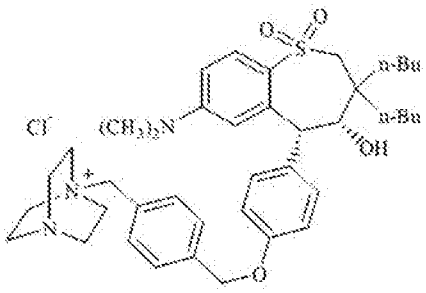
[00371] one or more R^x are independently selected from the group consisting of alkoxy, alkylamino and dialkylamino and –W-R^{31}, wherein W is O or NH and R^{31} is selected from

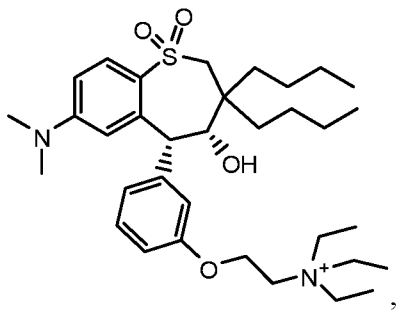
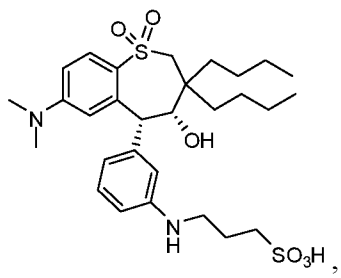
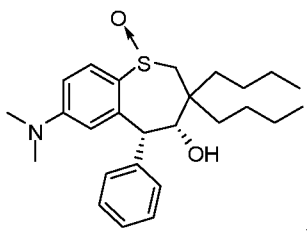

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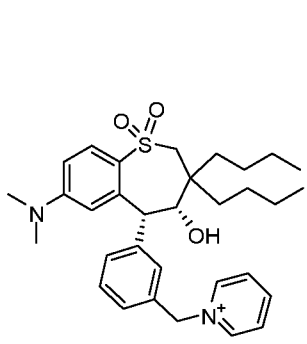
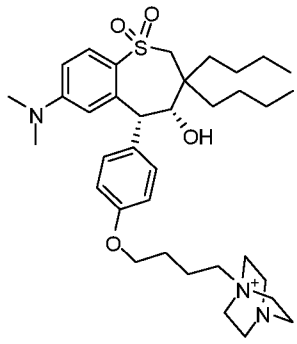
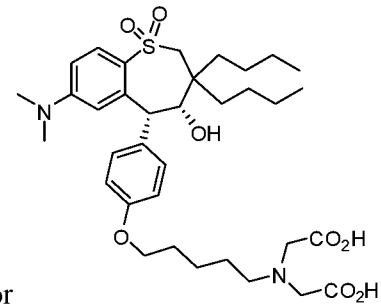

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and

;

[00372] or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

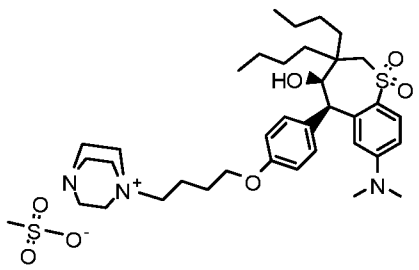
[00373] In some embodiments, a compound of Formula II is


,

(maralixibat),


,

,

,


,

, or

or the like.

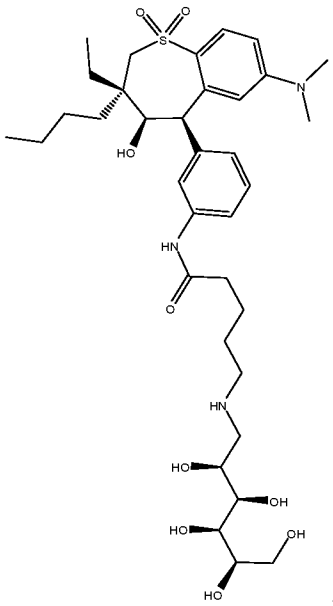
[00374] In some embodiments of the methods, the compound of Formula II is



[00375] .

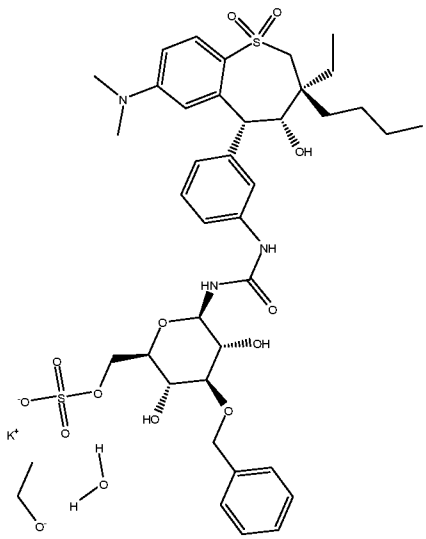
[00376] In certain embodiments, ASBTIs suitable for the methods described herein are non-systemic analogs of Compound 100C. Certain compounds provided herein are Compound 100C analogues modified or substituted to comprise a charged group. In specific embodiments, the Compound 100C analogues are modified or substituted with a charged group that is an ammonium group (e.g., a cyclic ar acyclic ammonium group). In certain embodiments, the ammonium group is a non-protic ammonium group that contains a quarternary nitrogen.

[00377] In some embodiments, a compound of Formula II is

[00378] .

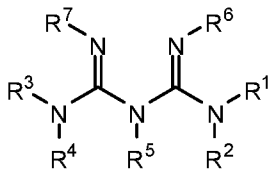
[00379] In some embodiments, a compound of Formula II is 1-[[5-[[3-[(3S,4R,5R)-3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5yl]phenyl]amino]-5-oxopentyl]amino]-1-deoxy-D-glucitol or SA HMR1741 (a.k.a. BARI-1741).

[00380] In some embodiments, a compound of Formula II is

[00381]  (volixibat potassium).

[00382] In some embodiments, a compound of Formula II is potassium((2R,3R,4S,5R,6R)-4-benzyloxy-6-{3-[3-((3S,4R,5R)-3-butyl-7-dimethylamino-3-ethyl-4-hydroxy-1,1-dioxo-2,3,4,5-tetrahydro-1H-benzo[b]thiepin-5-yl)-phenyl]-ureido}-3,5-dihydroxy-tetrahydro-pyran-2-ylmethyl)sulphate ethanolate, hydrate or SAR548304B (a.k.a. SAR-548304).

[00383] In some embodiments, an ASBTI suitable for the methods described herein is a compound of Formula III:

[00384]  Formula III

[00385] wherein:

[00386] each R^1, R^2 is independently H, hydroxy, alkyl, alkoxy, -C(=X)YR^8, -YC(=X)R^8, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted alkyl-aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkyl-cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkyl-heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted alkyl-heterocycloalkyl, or –L-K; or R^1 and R^2 together with the nitrogen to which they are attached form a 3-8-membered ring that is optionally susbtituted with R^8;

[00387] each R^3, R^4 is independently H, hydroxy, alkyl, alkoxy, -C(=X)YR^8, -YC(=X)R^8, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted alkyl-aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkyl-cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkyl-heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted alkyl-heterocycloalkyl, or –L-K;

[00388] R^5 is H, hydroxy, alkyl, alkoxy, -C(=X)YR^8, -YC(=X)R^8, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted alkyl-aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkyl-cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkyl-heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted alkyl-heterocycloalkyl,

[00389] each R^6, R^7 is independently H, hydroxy, alkyl, alkoxy, -C(=X)YR^8, -YC(=X)R^8, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted alkyl-aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkyl-cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkyl-heteroaryl, substituted or unsubstituted

heterocycloalkyl, substituted or unsubstituted alkyl-heterocycloalkyl, or –L-K; or R^6 and R^7 taken together form a bond;

[00390] each X is independently NH, S, or O;

[00391] each Y is independently NH, S, or O;

[00392] R^8 is substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted alkyl-aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkyl-cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkyl-heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted alkyl-heterocycloalkyl, or –L-K;

[00393] L is A_n, wherein

[00394] each A is independently NR^1, $S(O)_m$, O, C(=X)Y, Y(C=X), substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocycloalkyl; wherein each m is independently 0-2;

[00395] n is 0-7;

[00396] K is a moiety that prevents systemic absorption;

[00397] provided that at least one of R^1, R^2, R^3 or R^4 is –L-K;

[00398] or a pharmaceutically acceptable prodrug thereof.

[00399] In some embodiments of a compound of Formula III, R^1 and R^3 are –L-K. In some embodiments, R^1, R^2 and R^3 are –L-K.

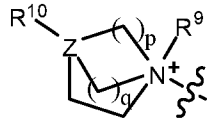
[00400] In some embodiments, at least one of R^1, R^2, R^3, R^4, R^5, R^6 and R^7 is H. In certain embodiments, R^5, R^6, R^7 are H and R^1, R^2, R^3 and R^4 are alkyl, aryl, alkyl-aryl, or heteroalkyl. In some embodiments, R^1 and R^2 are H. In some embodiments, R^1, R^2, R^5, R^6 and R^7 are H. In some embodiments, R^6 and R^7 together form a bond. In certain embodiments, R^5,R^6 and R^7 are H, alkyl or O-alkyl.

[00401] In some embodiments, R^1 and R^3 are –L-K. In some embodiments, R^1, R^2 and R^3 are –L-K. In some embodiments, R^3 and R^4 are –L-K. In some embodiments, R^1 and R^2 together with the nitrogen to which they are attached form a 3-8 membered ring and the ring is substituted with –L-K. In some embodiments, R^1 or R^2 or R^3 or R^4 are aryl optionally substituted with –L-K. In some embodiments, R^1 or R^2 or R^3 or R^4 are alkyl optionally substituted with –L-K. In some embodiments, R^1 or R^2 or R^3 or R^4 are alky-aryl optionally substituted with –L-K. In some embodiments, R^1 or R^2 or R^3 or R^4 are heteroalkyl optionally substituted with -L-K.

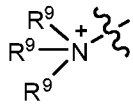
[00402] In some embodiments, L is a C_1-C_7alkyl. In some embodiments, L is heteroalkyl. In certain embodiments, L is C_1-C_7alkyl-aryl. In some embodiments, L is C_1-C_7alkyl-aryl- C_1-C_7alkyl.

[00403] In certain embodiments, K is a non-protic charged group. In some specific embodiments, each K is a ammonium group. In some embodiments, each K is a cyclic non-protic ammonium group. In some embodiments, each K is an acyclic non-protic ammonium group.

[00404] In certain embodiments, each K is a cyclic non-protic ammonium group of structure:



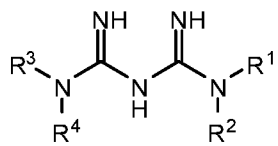
[00405] In certain embodiments, K is an acyclic non-protic ammonium group of structure:



[00406] wherein p, q, R^9, R^{10} and Z are as defined above. In certain embodiments, p is 1. In other embodiments, p is 2. In further embodimetns, p is 3. In some embodiments, q is 0. In other embodiments, q is 1. In some other embodiments, q is 2.

[00407] The compounds further comprise 1, 2, 3 or 4 anionic counterions selected from Cl^-, Br^-, I^-, $R^{11}SO_3^-$, $(SO_3^-\text{-}R^{11}\text{-}SO_3^-)$, $R^{11}CO_2^-$, $(CO_2^-\text{-}R^{11}\text{-}CO_2^-)$, $(R^{11})_2(P{=}O)O^-$ and $(R^{11})(P{=}O)O_2^{2-}$ wherein R^{11} is as defined above. In some embodiments, the counterion is Cl^-, Br^-, I^-, $CH_2CO_2^-$, $CH_3SO_3^-$, or $C_6H_5SO_3^-$ or CO_2^- - $(CH_2)_2$-CO_2^-. In some embodiments, the compound of Formula III has one K group and one counterion. In other embodiments, the compound of Formula III has one K group, and two molecules of the compound of Formula III have one counterion. In yet other embodiments, the compound of Formula III has two K groups and two counterions. In some other embodiments, the compound of Formula III has one K group comprising two ammonium groups and two counterions.

[00408] Also described herein are compounds having the Formula IIIA:



Formula IIIA

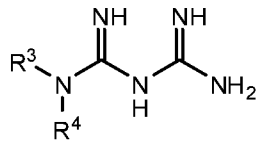
[00409] wherein:

[00410] each R^1, R^2 is independently H, substituted or unsubstituted alkyl, or –L-K; or R^1 and R^2 together with the nitrogen to which they are attached form a 3-8-membered ring that is optionally susbtituted with R^8;

[00411] and R^3, R^4, R^8, L and K are as defined above.

[00412] In some embodiments of compounds of Formula IIIA, L is A_n, wherein each A is substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl, and n is 0-7. In certain specific embodiments of the compound of Formula IIIA, R^1 is H. In some embodiments of Formula IIIA, R^1 and R^2 together with the nitrogen to which they are attached form a 3-8-membered ring that is optionally susbtituted with –L-K.

[00413] Also described herein are compounds having the Formula IIIB:



Formula IIIB

[00414] wherein:

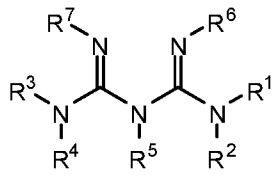
[00415] each R^3, R^4 is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted alkyl-aryl, or –L-K;

[00416] and R^1, R^2, L and K are as defined above.

[00417] In certain embodiments of Formula IIIB, R^3 is H. In certain embodiments, R^3 and R^4 are each –L-K. In some embodiments, R^3 is H and R^4 is substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted alkyl-aryl containing one or two –L-K groups.

[00418] In some embodiments, an ASBTI suitable for the methods described herein is a compound of Formula IIIC

[00419]



Formula IIIC

[00420] wherein:

[00421] each R^1, R^2 is independently H, hydroxy, alkyl, alkoxy, -C(=X)YR^8, -YC(=X)R^8, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted alkyl-aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkyl-cycloalkyl,

substituted or unsubstituted heteroaryl, substituted or unsubstituted alkyl-heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted alkyl-heterocycloalkyl, or –L-K; or R^1 and R^2 together with the nitrogen to which they are attached form a 3-8-membered ring that is optionally susbtituted with R^8;

[00422] each R^3, R^4 is independently H, hydroxy, alkyl, alkoxy, -C(=X)YR^8, -YC(=X)R^8, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted alkyl-aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkyl-cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkyl-heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted alkyl-heterocycloalkyl, or –L-K;

[00423] R^5 is H, hydroxy, alkyl, alkoxy, -C(=X)YR^8, -YC(=X)R^8, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted alkyl-aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkyl-cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkyl-heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted alkyl-heterocycloalkyl,

[00424] each R^6, R^7 is independently H, hydroxy, alkyl, alkoxy, -C(=X)YR^8, -YC(=X)R^8, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted alkyl-aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkyl-cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkyl-heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted alkyl-heterocycloalkyl, or –L-K; or R^6 and R^7 taken together form a bond;

[00425] each X is independently NH, S, or O;

[00426] each Y is independently NH, S, or O;

[00427] R^8 is substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted alkyl-aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkyl-cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkyl-heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted alkyl-heterocycloalkyl, or –L-K;

[00428] L is A_n, wherein

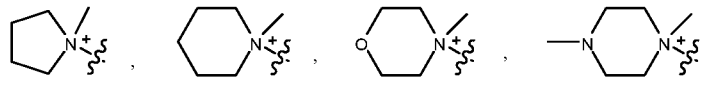
[00429] each A is independently NR^1, $S(O)_m$, O, C(=X)Y, Y(C=X), substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocycloalkyl; wherein each m is independently 0-2;

[00430] n is 0-7;

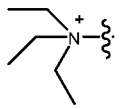
[00431] K is a moiety that prevents systemic absorption;

[00432] or a pharmaceutically acceptable salt thereof.

[00433] In some specific embodiments of Formula I, II or III, K is selected from

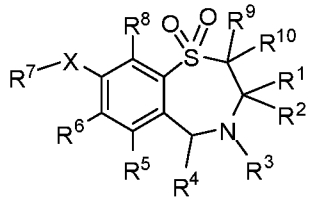


and



[00434]

[00435] In some embodiments, an ASBTI suitable for the methods described herein is a compound of Formula IV:



[00436] IV

[00437] wherein

[00438] R^1 is a straight chain C_{1-6} alkyl group;

[00439] R^2 is a straight chain C_{1-6} alkyl group;

[00440] R^3 is hydrogen or a group OR^{11} in which R^{11} is hydrogen, optionally substituted C_{1-6} alkyl or a C_{1-6} alkylcarbonyl group;

[00441] R^4 is pyridyl or an optionally substituted phenyl;

[00442] R^5, R^6 and R^8 are the same or different and each is selected from:

[00443] hydrogen, halogen, cyano, R^{15} -acetylide, OR^{15}, optionally substituted C_{1-6} alkyl, COR^{15}, $CH(OH)R^{15}$, $S(O)_nR^{15}$, $P(O)(OR^{15})_2$, $OCOR^{15}$, OCF_3, OCN, SCN, NHCN, CH_2OR^{15}, CHO, $(CH_2)_pCN$, $CONR^{12}R^{13}$, $(CH_2)_pCO_2R^{15}$, $(CH_2)_pNR^{12}R^{13}$, CO_2R^{15}, $NHCOCF_3$, $NHSO_2R^{15}$, OCH_2OR^{15}, $OCH{=}CHR^{15}$, $O(CH_2CH_2O)_nR^{15}$, $O(CH_2)_pSO_3R^{15}$, $O(CH_2)_pNR^{12}R^{13}$ and $O(CH_2)_pN^+R^{12}R^{13}R^{14}$ wherein

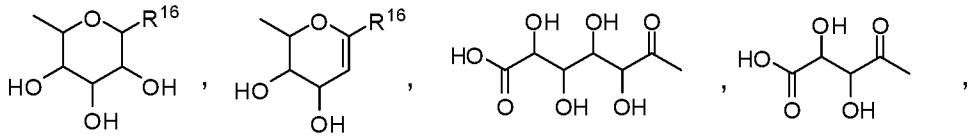
[00444] p is an integer from 1–4,

[00445] n is an integer from 0–3 and

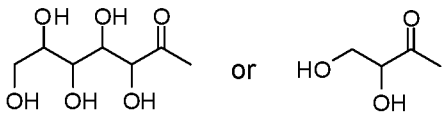
[00446] R^{12}, R^{13}, R^{14} and R^{15} are independently selected from hydrogen and optionally substituted C^{1-6} alkyl;

[00447] R^7 is a group of the formula

[00448]



[00449]



[00450]

[00451] wherein the hydroxyl groups may be substituted by acetyl, benzyl,

[00452] or —(C_1–C_6)-alkyl-R^{17},

[00453] wherein the alkyl group may be substituted with one or more hydroxyl groups;

[00454] R^{16} is —COOH, —CH_2—OH, —CH_2—O-Acetyl, —COOMe or —COOEt;

[00455] R^{17} is H, —OH, —NH_2, —COOH or $COOR^{18}$;

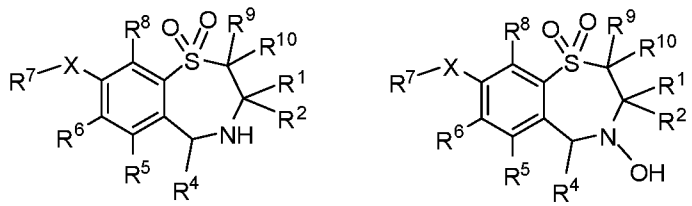
[00456] R^{18} is (C_1–C_4)-alkyl or —NH—(C_1–C_4)-alkyl;

[00457] X is —NH—or —O—; and

[00458] R^9 and R^{10} are the same or different and each is hydrogen or C_1-C_6 alkyl; and salts thereof.

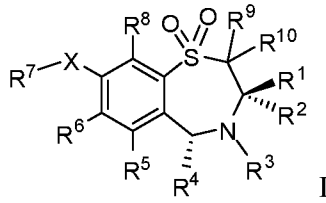
[00459] In some embodiments, a compound of Formula IV has the structure of Formula IVA or Formula IVB:

[00460]

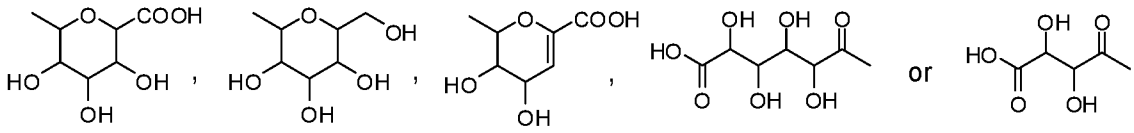


[00461] Formula IVA Formula IVB

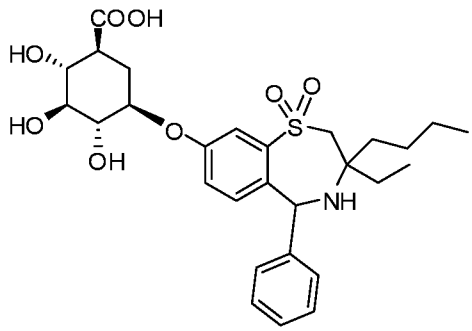
[00462] In some embodiments, a compound of Formula IV has the structure of Formula IVC:

[00463]  IVC

[00464] In some embodiments of Formula IV, X is O and R^7 is selected from

[00465] 

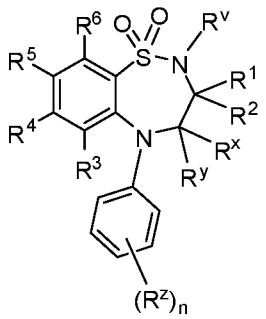
[00466] In some embodiments, a compound of Formula IV is:

[00467] 

[00468]

[00469] In some embodiments, an ASBTI suitable for the methods described herein is a compound of Formula V:

[00470]

[00471]  V

[00472] wherein:

[00473] R^v is selected from hydrogen or C_{1-6}alkyl;

[00474] One of R^1 and R^2 are selected from hydrogen or C_{1-6}alkyl and the other is selected from C_{1-6}alkyl;

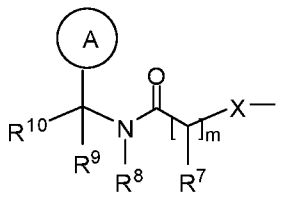
[00475] R^x and R^y are independently selected from hydrogen, hydroxy, amino, mercapto, C_{1-6}alkyl, C_{1-6}alkoxy, N—(C_{1-6}alkyl)amino, N,N—(C_{1-6}alkyl)$_2$amino, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2;

[00476] R^z is selected from halo, nitr, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, N—(C_{1-6}alkyl)amino, N,N—(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, N—(C_{1-6}alkyl)carbamoyl, N,N—(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, N—(C_{1-6}-alkyl)sulphamoyl and N,N—(C_{1-6}alkyl)$_2$sulphamoyl;

[00477] n is 0–5;

[00478] one of R^4 and R^5 is a group of formula (VA):

[00479]



VA

[00480] R^3 and R^6 and the other of R^4 and R^5 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, N—(C_{1-6}alkyl)amino, N,N—(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, N—(C_{1-6}alkyl)carbamoyl, N,N—(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, N—(C_{1-6}alkyl)sulphamoyl and N,N—(C_{1-6}alkyl)$_2$sulphamoyl;

[00481] wherein R^3 and R^6 and the other of R^4 and R^5 may be optionally substituted on carbon by one or more R^{17};

[00482] X is —O—, —N(R^a)—, —S(O)$_b$— or —CH(R^a)—;

[00483] wherein R^a is hydrogen or C_{1-6}alkyl and b is 0–2;

[00484] Ring A is aryl or heteroaryl;

[00485] wherein Ring A is optionally substituted on carbon by one or more substituents selected from R^{18};

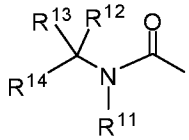
[00486] R^7 is hydrogen, C_{1-6}alkyl, carbocyclyl or heterocyclyl;

[00487] wherein R^7 is optionally substituted on carbon by one or more substituents selected from R^{19}; and wherein if said heterocyclyl contains an —NH— group, that nitrogen may be optionally substituted by a group selected from R^{20};

[00488] R^8 is hydrogen or C_{1-6}-alkyl;

[00489] R^9 is hydrogen or C_{1-6}alkyl;

[00490] R^{10} is hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, C_{1-10}alkyl, C_{2-10}alkynyl, C_{2-10}alkynyl, C_{1-10}alkoxy, C_{1-10}alkanoyl, C_{1-10}alkanoyloxy, N—(C_{1-10}alkyl)amino, N,N—(C_{1-10}alkyl)$_2$amino, N,N,N—(C_{1-10}alkyl)$_3$ammonio, C_{1-10}alkanoylamino, N—(C_{1-10}alkyl)carbamoyl, N,N—(C_{1-10}alkyl)$_2$carbamoyl, C_{1-10}alkylS(O)$_a$ wherein a is 0 to 2, N—(C_{1-10}alkyl)sulphamoyl, N,N—(C_{1-10}alkyl)$_2$sulphamoyl, N—(C_{1-10}alkyl)sulphamoylamino, N,N—(C_{1-10}alkyl)$_2$sulphamoylamino, C_{1-10}alkoxycarbonylamino, carbocyclyl, carbocyclylC_{1-10}alkyl, heterocyclyl, heterocyclylC_{1-10}alkyl, carbocyclyl-(C_{1-10}alkylene)$_p$-R^{21}—(C_{1-10}alkylene)$_q$- or heterocyclyl-(C_{1-10}alkylene)$_r$-R^{22}—(C_{1-10}alkylene)$_s$-; wherein R^{10} is optionally substituted on carbon by one or more substituents selected from R^{23}; and wherein if said heterocyclyl contains an —NH— group, that nitrogen may be optionally substituted by a group selected from R^{24}; or R^{10} is a group of formula (VB):

[00491]  VB

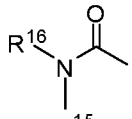
[00492] wherein:

[00493] R^{11} is hydrogen or C_{1-6}-alkyl;

[00494] R^{12} and R^{13} are independently selected from hydrogen, halo, carbamoyl, sulphamoyl, C_{1-10}alkyl, C_{2-10}alkynyl, C_{2-10}alkynyl, C_{1-10}alkanoyl, N—(C_{1-10}alkyl)carbamoyl, N,N—(C_{1-10}alkyl)$_2$carbamoyl, C_{1-10}alkylS(O)$_a$ wherein a is 0 to 2, N—(C_{1-10}alkyl)sulphamoyl, N,N—(C_{1-10}alkyl)$_2$sulphamoyl, N—(C_{1-10}alkyl)sulphamoylamino, N,N—(C_{1-10}alkyl)$_2$sulphamoylamino, carbocyclyl or heterocyclyl; wherein R^{12} and R^{13} may be independently optionally substituted on carbon by one or more substituents selected from R^{25}; and wherein if said heterocyclyl contains an —NH— group, that nitrogen may be optionally substituted by a group selected from R^{26};

[00495] R^{14} is selected from hydrogen, halo, carbamoyl, sulphamoyl, hydroxyaminocarbonyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkanoyl, N—(C_{1-10}alkyl)carbamoyl, N,N—(C_{1-10}alkyl)$_2$carbamoyl, C_{1-10}alkylS(O)$_a$ wherein a is 0 to 2, N—(C_{1-10}alkyl)sulphamoyl, N,N—(C_{1-10}alkyl)$_2$sulphamoyl, N—(C_{1-10}alkyl)sulphamoylamino, N,N—(C_{1-10}alkyl)$_2$sulphamoylamino, carbocyclyl, carbocyclylC_{1-10}alkyl, heterocyclyl, heterocyclylC_{1-10}alkyl, carbocyclyl-(C_{1-10}alkylene)$_p$-R^{27}—(C_{1-10}alkylene)$_q$- or heterocyclyl-(C_{1-10}alkylene)$_r$-R^{28}—(C_{1-10}alkylene)$_s$-; wherein R^{14} may be optionally substituted on carbon by one or more substituents selected from R^{29}; and wherein if said heterocyclyl contains an

—NH— group, that nitrogen may be optionally substituted by a group selected from R^{30}; or R^{14} is a group of formula (VC):



[00496] VC

[00497] R^{15} is hydrogen or C_{1-6}alkyl; and R^{16} is hydrogen or C_{1-6}alkyl; wherein R^{16} may be optionally substituted on carbon by one or more groups selected from R^{31};

[00498] or R^{15} and R^{16} together with the nitrogen to which they are attached form a heterocyclyl; wherein said heterocyclyl may be optionally substituted on carbon by one or more R^{37}; and wherein if said heterocyclyl contains an —NH— group, that nitrogen may be optionally substituted by a group selected from R^{38};

[00499] m is 1–3; wherein the values of R^7 may be the same or different;

[00500] R^{17}, R^{18}, R^{19}, R^{23}, R^{25}, R^{29}, R^{31} and R^{37} are independently selected from halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxy, C_{1-10}alkanoyl, C_{1-10}alkanoyloxy, N—(C_{1-10}alkyl)amino, N,N—(C_{1-10}alkyl)$_2$amino, N,N,N—(C_{1-10}alkyl)$_3$ammonio, C_{1-10}alkanoylamino, N—(C_{1-10}alkyl)carbamoyl, N,N—(C_{1-10}alkyl)$_2$carbamoyl, C_{1-10}alkylS(O)$_a$ wherein a is 0 to 2, N—(C_{1-10}alkyl)sulphamoyl, N,N—(C_{1-10}alkyl)$_2$sulphamoyl, N—(C_{1-10}alkyl)sulphamoylamino, N,N—(C_{1-10}alkyl)$_2$sulphamoylamino, C_{1-10}alkoxycarbonylamino, carbocyclyl, carbocyclylC_{1-10}alkyl, heterocyclyl, heterocyclylC_{1-10}alkyl, carbocyclyl-(C_{1-10}alkylene)$_p$-R^{32}—(C_{1-10}alkylene)$_q$- or heterocyclyl-(C_{1-10}alkylene)$_r$-R^{33}—(C_{1-10}alkylene)$_s$-; wherein R^{17}, R^{18}, R^{19}, R^{23}, R^{25}, R^{29}, R^{31} and R^{37} may be independently optionally substituted on carbon by one or more R^{34}; and wherein if said heterocyclyl contains an —NH— group, that nitrogen may be optionally substituted by a group selected from R^{35};

[00501] R^{21}, R^{22}, R^{27}, R^{28}, R^{32} or R^{33} are independently selected from —O—, —NR^{36}—, —$S(O)_x$—, —$NR^{36}C(O)NR^{36}$—, —$NR^{36}C(S)NR^{36}$—, —OC(O)N=C—, —$NR^{36}C(O)$— or —$C(O)NR^{36}$—; wherein R^{36} is selected from hydrogen or C_{1-6}alkyl, and x is 0–2;

[00502] p, q, r and s are independently selected from 0–2;

[00503] R^{34} is selected from halo, hydroxy, cyano, carbamoyl, ureido, amino, nitro, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, methyl, ethyl, methoxy, ethoxy, vinyl, allyl, ethynyl, formyl, acetyl, formamido, acetylamino, acetoxy, methylamino, dimethylamino, N-methylcarbamoyl, N,N-dimethylcarbamoyl, methylthio, methylsulphinyl,

mesyl, N-methylsulphamoyl, N,N-dimethylsulphamoyl, N-methylsulphamoylamino and N,N-dimethylsulphamoylamino;

[00504] R^{20}, R^{24}, R^{26}, R^{30}, R^{35} and R^{38} are independently selected from C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, N—(C_{1-6}alkyl)carbamoyl, N,N—(C_{1-6}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl; and

[00505] wherein a "heteroaryl" is a totally unsaturated, mono or bicyclic ring containing 3–12 atoms of which at least one atom is chosen from nitrogen, sulphur and oxygen, which heteroaryl may, unless otherwise specified, be carbon or nitrogen linked;

[00506] wherein a "heterocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 3–12 atoms of which at least one atom is chosen from nitrogen, sulphur and oxygen, which heterocyclyl may, unless otherwise specified, be carbon or nitrogen linked, wherein a —CH_2- group can optionally be replaced by a —C(O)— group, and a ring sulphur atom may be optionally oxidised to form an S-oxide; and

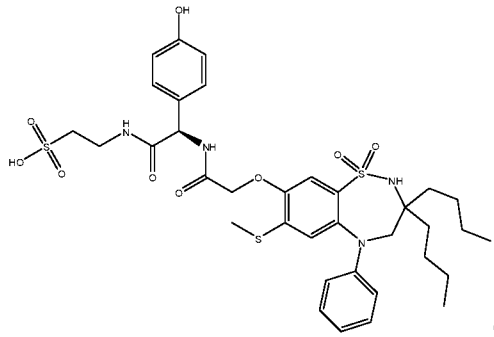
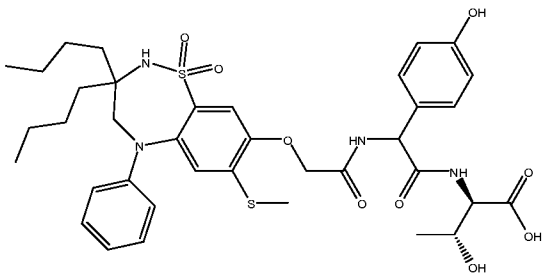
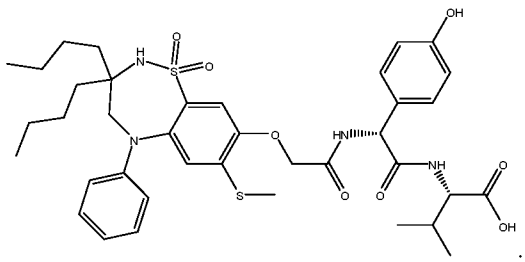
[00507] wherein a "carbocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic carbon ring that contains 3–12 atoms; wherein a —CH_2- group can optionally be replaced by a —C(O) group;

[00508] or a pharmaceutically acceptable salt or in vivo hydrolysable ester or amide formed on an available carboxy or hydroxy group thereof.

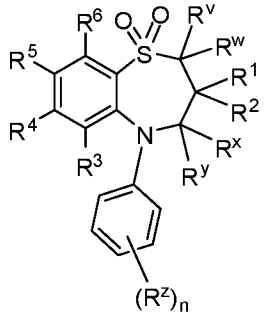
[00509] In some embodiments, compound of Formula V is 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N-((R)-1-carboxy-2-methylthio-ethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)- α-[N-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-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)-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)-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, or a salt thereof.

[00510] In some embodiments, compound of Formula V is

[00511]  or  or .

[00512] In some embodiments, an ASBTI suitable for the methods described herein is a compound of Formula VI:



[00513] VI

[00514] wherein:

[00515] R^v and R^w are independently selected from hydrogen or C_{1-6}alkyl;

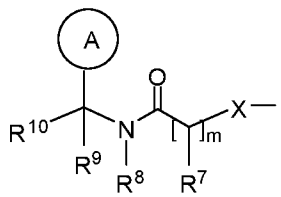
[00516] one of R^1 and R^2 is selected from hydrogen or C_{1-6}alkyl and the other is selected from C_{1-6}alkyl;

[00517] R^x and R^y are independently selected from hydrogen or C_{1-6}alkyl, or one of R^x and R^y is hydrogen or C_{1-6}alkyl and the other is hydroxy or C_{1-6}alkoxy;

[00518] R^z is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, N—(C_{1-6}alkyl)amino, N,N—(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, N—(C_{1-6}alkyl)carbamoyl, N,N—(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, N—(C_{1-6}alkyl)sulphamoyl and N,N—(C_{1-6}alkyl)$_2$sulphamoyl;

[00519] n is 0–5;

[00520] one of R^4 and R^5 is a group of formula (VIA):



[00521] VIA

[00522] R^3 and R^6 and the other of R^4 and R^5 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, N—(C_{1-6}alkyl)amino, N,N—(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, N—(C_{1-6}alkyl)carbamoyl, N,N—(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, N—(C_{1-6}alkyl)sulphamoyl and N,N—(C_{1-6}alkyl)$_2$sulphamoyl; wherein R^3 and R^6 and the other of R^4 and R^5 may be optionally substituted on carbon by one or more R^{17};

[00523] X is —O—, —N(R^a)—, —S(O)$_b$— or —CH(R^a)—; wherein R^a is hydrogen or C_{1-6}alkyl and b is 0–2;

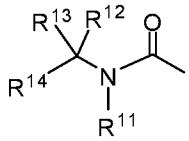
[00524] Ring A is aryl or heteroaryl; wherein Ring A is optionally substituted on carbon by one or more substituents selected from R^{18};

[00525] R^7 is hydrogen, C_{1-6}alkyl, carbocyclyl or heterocyclyl; wherein R^7 is optionally substituted on carbon by one or more substituents selected from R^{19}; and wherein if said heterocyclyl contains an —NH— group, that nitrogen may be optionally substituted by a group selected from R^{20};

[00526] R^8 is hydrogen or C_{1-6}alkyl;

[00527] R^9 is hydrogen or C_{1-6}alkyl;

[00528] R^{10} is hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxy, C_{1-10}alkanoyl, C_{1-10}alkanoyloxy, N—(C_{1-10}alkyl)amino, N,N—(C_{1-10}alkyl)$_2$amino, N,N,N—(C_{1-10}alkyl)$_3$ammonio, C_{1-10}alkanoylamino, N—(C_{1-10}alkyl)carbamoyl, N,N—(C_{1-10}alkyl)$_2$carbamoyl, C_{1-10}alkylS(O)$_a$ wherein a is 0 to 2, N—(C_{1-10}alkyl)sulphamoyl, N,N—(C_{1-10}alkyl)$_2$sulphamoyl, N—(C_{1-10}alkyl)sulphamoylamino, N,N—(C_{1-10}alkyl)$_2$sulphamoylamino, C_{1-10}alkoxycarbonylamino, carbocyclyl, carbocyclylC_{1-10}alkyl, heterocyclyl, heterocyclylC_{1-10}alkyl, carbocyclyl-(C_{1-10}alkylene)$_p$-R^{21}—(C_{1-10}alkylene)$_q$- or heterocyclyl-(C_{1-10}alkylene)$_r$-R^{22}—(C_{1-10}alkylene)$_s$-; wherein R^{10} is optionally substituted on carbon by one or more substituents selected from R^{23}; and wherein if said heterocyclyl contains an —NH— group, that nitrogen may be optionally substituted by a group selected from R^{24}; or R^{10} is a group of formula (VIB):

[00529]  VIB

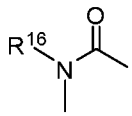
[00530] wherein:

[00531] R^{11} is hydrogen or C_{1-6}alkyl;

[00532] R^{12} and R^{13} are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxy, C_{1-10}alkanoyl, C_{1-10}alkanoyloxy, N—(C_{1-10}alkyl)amino, N,N—(C_{1-10}alkyl)$_2$amino, C_{1-10}alkanoylamino, N—(C_{1-10}alkyl)carbamoyl, N,N—(C_{1-10}alkyl)$_2$carbamoyl, C_{1-10}alkylS(O)$_a$ wherein a is 0 to 2, N—(C_{1-10}alkyl)sulphamoyl, N,N—(C_{1-10}alkyl)$_2$sulphamoyl, N—(C_{1-10}alkyl)sulphamoylamino, N,N—(C_{1-10}alkyl)$_2$sulphamoylamino, carbocyclyl or heterocyclyl; wherein R^{12} and R^{13} may be independently optionally substituted on carbon by one or more

substituents selected from R^{25}; and wherein if said heterocyclyl contains an —NH— group, that nitrogen may be optionally substituted by a group selected from R^{26};

[00533] R^{14} is selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxy, C_{1-10}alkanoyl, C_{1-10}alkanoyloxy, N—(C_{1-10}alkyl)amino, N,N—(C_{1-10}alkyl)$_2$amino, N,N,N—(C_{1-10}alkyl)$_3$ammonio, C_{1-10}alkanoylamino, N—(C_{1-10}alkyl)carbamoyl, N,N—(C_{1-10}alkyl)$_2$carbamoyl, C_{1-10}alkylS(O)$_a$ wherein a is 0 to 2, N—(C_{1-10}alkyl)sulphamoyl, N,N—(C_{1-10}alkyl)$_2$sulphamoyl, N—(C_{1-10}alkyl)sulphamoylamino, N,N—(C_{1-10}alkyl)$_2$sulphamoylamino, C_{1-10}alkoxycarbonylamino, carbocyclyl, carbocyclylC_{1-10}alkyl, heterocyclyl, heterocyclylC_{1-10}alkyl, carbocyclyl-(C_{1-10}alkylene)$_p$-R^{27}—(C_{1-10}alkylene)$_q$- or heterocyclyl-(C_{1-10}alkylene)$_r$-R^{28}—(C_{1-10}alkylene)$_s$-; wherein R^{14} may be optionally substituted on carbon by one or more substituents selected from R^{29}; and wherein if said heterocyclyl contains an —NH— group, that nitrogen may be optionally substituted by a group selected from R^{30}; or R^{14} is a group of formula (VIC):



[00534] VIC

[00535] R^{15} is hydrogen or C_{1-6}alkyl;

[00536] R^{16} is hydrogen or C_{1-6}alkyl; wherein R^{16} may be optionally substituted on carbon by one or more groups selected from R^{31};

[00537] n is 1–3; wherein the values of R^7 may be the same or different;

[00538] R^{17}, R^{18}, R^{19}, R^{23}, R^{25}, R^{29} or R^{31} are independently selected from halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, amidino, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxy, C_{1-10}alkanoyl, C_{1-10}alkanoyloxy, (C_{1-10}alkyl)$_3$silyl, N—(C_{1-10}alkyl)amino, N,N—(C_{1-10}alkyl)$_2$amino, N,N,N—(C_{1-10}alkyl)$_3$ammonio, C_{1-10}alkanoylamino, N—(C_{1-10}alkyl)carbamoyl, N,N—(C_{1-10}alkyl)$_2$carbamoyl, C_{1-10}alkylS(O)$_a$ wherein a is 0 to 2, N—(C_{1-10}alkyl)sulphamoyl, N,N—(C_{1-10}alkyl)$_2$sulphamoyl, N—(C_{1-10}alkyl)sulphamoylamino, N,N—(C_{1-10}alkyl)$_2$sulphamoylamino, C_{1-10}alkoxycarbonylamino, carbocyclyl, carbocyclylC_{1-10}alkyl, heterocyclyl, heterocyclylC_{1-10}alkyl, carbocyclyl-(C_{1-10}alkylene)$_p$-R^{32}—(C_{1-10}alkylene)$_q$- or heterocyclyl-(C_{1-10}alkylene)$_r$-R^{33}—(C_{1-10}alkylene)$_s$-; wherein R^{17}, R^{18}, R^{19}, R^{23}, R^{25}, R^{29} or R^{31} may be independently optionally substituted on carbon by one or more R^{34}; and wherein

if said heterocyclyl contains an —NH— group, that nitrogen may be optionally substituted by a group selected from R^{35};

[00539] R^{21}, R^{22}, R^{27}, R^{28}, R^{32} or R^{33} are independently selected from —O—, —NR^{36}—, —$S(O)_x$—, —$NR^{36}C(O)NR^{36}$—, —$NR^{36}C(S)NR^{36}$—, —$OC(O)N{=}C$—, —$NR^{36}C(O)$— or —$C(O)NR^{36}$—; wherein R^{36} is selected from hydrogen or $C_{1\text{-}6}$alkyl, and x is 0–2;

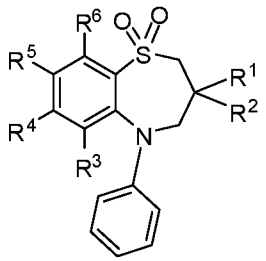
[00540] p, q, r and s are independently selected from 0–2;

[00541] R^{34} is selected from halo, hydroxy, cyano, carbamoyl, ureido, amino, nitro, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, methyl, ethyl, methoxy, ethoxy, vinyl, allyl, ethynyl, formyl, acetyl, formamido, acetylamino, acetoxy, methylamino, dimethylamino, N-methylcarbamoyl, N,N-dimethylcarbamoyl, methylthio, methylsulphinyl, mesyl, N-methylsulphamoyl, N,N-dimethylsulphamoyl, N-methylsulphamoylamino and N,N-dimethylsulphamoylamino;

[00542] R^{20}, R^{24}, R^{26}, R^{30} or R^{35} are independently selected from $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkanoyl, $C_{1\text{-}6}$alkylsulphonyl, $C_{1\text{-}6}$alkoxycarbonyl, carbamoyl, N—($C_{1\text{-}6}$alkyl)carbamoyl, N,N—($C_{1\text{-}6}$alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

[00543] or a pharmaceutically acceptable salt, solvate or solvate of such a salt, or an in vivo hydrolysable ester formed on an available carboxy or hydroxy thereof, or an in vivo hydrolysable amide formed on an available carboxy thereof.

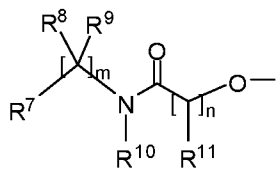
[00544] In some embodiments, a compound of Formula VI has the structure of Formula VID:



[00545] VID

[00546] wherein:

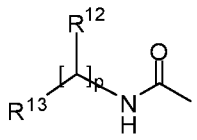
[00547] R^1 and R^2 are independently selected from $C_{1\text{-}6}$alkyl; one of R^4 and R^5 is a group of formula (VIE):



[00548] VIE

[00549] R^3 and R^6 and the other of R^4 and R^5 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, N-(C_{1-4}alkyl)amino, N,N-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, N-(C_{1-4}alkyl)carbamoyl, N,N-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, N-(C_{1-4}alkyl)sulphamoyl and N,N-(C_{1-4}alkyl)$_2$sulphamoyl; wherein R^3 and R^6 and the other of R^4 and R^5 may be optionally substituted on carbon by one or more R^{14};

[00550] R^7 is carboxy, sulpho, sulphino, phosphono, —P(O)(OR^a)(OR^b), P(O)(OH)(OR$_a$), —P(O)(OH)(R^a) or P(O)(OR^a)(R^b), wherein R^a and R^b are independently selected from C_{1-6}alkyl; or R^7 is a group of formula (VIF):

[00551]  VIF

[00552] R^8 and R^9 are independently hydrogen, C_{1-4}alkyl or a saturated cyclic group, or R^8 and R^9 together form C_{2-6}alkylene; wherein R^8 and R^9 or R^8 and R^9 together may be independently optionally substituted on carbon by one or more substituents selected from R^{15}; and wherein if said saturated cyclic group contains an —NH— moiety, that nitrogen may be optionally substituted by one or more R^{20};

[00553] R^{10} is hydrogen or C_{1-4}alkyl; wherein R^{10} is optionally substituted on carbon by one or more substituents selected from R^{24};

[00554] R^{11} is hydrogen, C^{1-4}alkyl, carbocyclyl or heterocyclyl; wherein R^{11} is optionally substituted on carbon by one or more substituents selected from R^{16}; and wherein if said heterocyclyl contains an —NH— moiety, that nitrogen may be optionally substituted by one or more R^{21};

[00555] R^{12} is hydrogen or C_{1-4}alkyl, carbocyclyl or heterocyclyl; wherein R^{12} optionally substituted on carbon by one or more substituents selected from R^{17}; and wherein if said heterocyclyl contains an —NH— moiety, that nitrogen may be optionally substituted by one or more R^{22};

[00556] R^{13} is carboxy, sulpho, sulphino, phosphono, —P(O)(OR^c)(OR^d), —P(O)(OH)(OR^c), —P(O)(OH)(R^c) or —P(O)(OR^c)(R^d) wherein R^c and R^d are independently selected from C_{1-6}alkyl;

[00557] m is 1–3; wherein the values of R^8 and R^9 may be the same or different;

[00558] n is 1–3; wherein the values of R^{11} may be the same or different;

[00559] p is 1–3; wherein the values of R^{12} may be the same or different;

[00560] R^{14} and R^{16} are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, N-(C_{1-4}alkyl)amino, N,N-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, N-(C_{1-4}alkyl)carbamoyl, N,N-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, N-(C_{1-4}alkyl)sulphamoyl and N,N-(C_{1-4}alkyl)$_2$sulphamoyl; wherein R^{14} and R^{16} may be independently optionally substituted on carbon by one or more R^{18};

[00561] R^{15} and R^{17} are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, N-(C_{1-4}alkyl)amino, N,N-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, N-(C_{1-4}alkyl)carbamoyl, N,N-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, N-(C_{1-4}alkyl)sulphamoyl and N,N-(C_{1-4}alkyl)$_2$sulphamoyl, carbocyclyl, heterocyclyl, sulpho, sulphino, amidino, phosphono, —P(O)(OR^e)(OR^f), —P(O)(OH)(OR^e), —P(O)(OH)(R^e) or —P(O)(OR^e)(R^f), wherein R^e and R^f are independently selected from C_{1-6}alkyl; wherein R^{15} and R^{17} may be independently optionally substituted on carbon by one or more R^{19}; and wherein if said heterocyclyl contains an —NH— moiety, that nitrogen may be optionally substituted by one or more R^{23};

[00562] R^{18}, R^{19} and R^{25} are independently selected from halo, hydroxy, cyano, carbamoyl, ureido amino nitro, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, methyl, ethyl, methoxy, ethoxy, vinyl, allyl, ethynyl, methoxycarbonyl, formyl, acetyl, formamido, acetylamino, acetoxy, methylamino, dimethylamino, N-methylcarbamoyl, N,N-dimethylcarbamoyl, methylthio, methylsulphinyl, mesyl, N-methylsulphamoyl and N,N-dimethylsulphamoyl;

[00563] R^{20}, R^{21}, R^{22}, R^{23} and R^{26} are independently C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, sulphamoyl, N-(C_{1-4}alkyl)sulphamoyl, N,N-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkoxycarbonyl, carbamoyl, N-(C_{1-4}alkyl)carbamoyl, N,N-(C_{1-4}alkyl)$_2$carbamoyl, benzyl, phenethyl, benzoyl, phenylsulphonyl and phenyl;

[00564] R^{24} is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, N-(C_{1-4}alkyl)amino, N,N-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, N-(C_{1-4}alkyl)carbamoyl, N,N-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, N-(C_{1-4}alkyl)sulphamoyl and N,N-(C_{1-4}alkyl)$_2$sulphamoyl, carbocyclyl,

heterocyclyl; wherein R^{24} may be independently optionally substituted on carbon by one or more R^{25}; and wherein if said heterocyclyl contains an —NH— moiety, that nitrogen may be optionally substituted by one or more R^{26};

[00565] wherein any saturated cyclic group is a totally or partially saturated, mono or bicyclic ring containing 3-12 atoms of which 0-4 atoms are chosen from nitrogen, sulphur or oxygen, which may be carbon or nitrogen linked;

[00566] wherein any heterocyclyl is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 3-12 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may be carbon or nitrogen linked, wherein a —CH_2— group can optionally be replaced by a —C(O)— or a ring sulphur atom may be optionally oxidised to form the S-oxides; and

[00567] wherein any carbocyclyl is a saturated, partially saturated or unsaturated, mono or bicyclic carbon ring that contains 3-12 atoms, wherein a —CH_2— group can optionally be replaced by a —C(O)—;

[00568] or a pharmaceutically acceptable salt thereof.

[00569] In some embodiments, a compound of Formula IV is 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)-1-carboxyethyl)carbamoyl]benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; or a salt thereof.

[00570] In some embodiments, any compound described herein is covalently conjugated to a bile acid using any suitable method. In some embodiments, compounds described herein are covalently bonded to a cyclodextrin or a biodegradable polymer (e.g., a polysaccharide).

[00571] In certain embodiments compounds described herein are not systemically absorbed. Moreover, provided herein are compounds that inhibit bile salt recycling in the gastrointestinal tract of an individual. In some embodiments, compounds described herein, may not be transported from the gut lumen and/or do not interact with ASBT. In some embodiments, compounds described herein, do not affect, or minimally affect, fat digestion and/or absorption. In certain embodiments, the administration of a therapeutically effective

amount of any compound described herein does not result in gastrointestinal disturbance or lactic acidosis in an individual. In certain embodiments, compounds described herein are administered orally. In some embodiments, an ASBTI is released in the distal ileum. An ASBTI compatible with the methods described herein may be a direct inhibitor, an allosteric inhibitor, or a partial inhibitor of the Apical Sodium-dependent Bile acid Transporter.

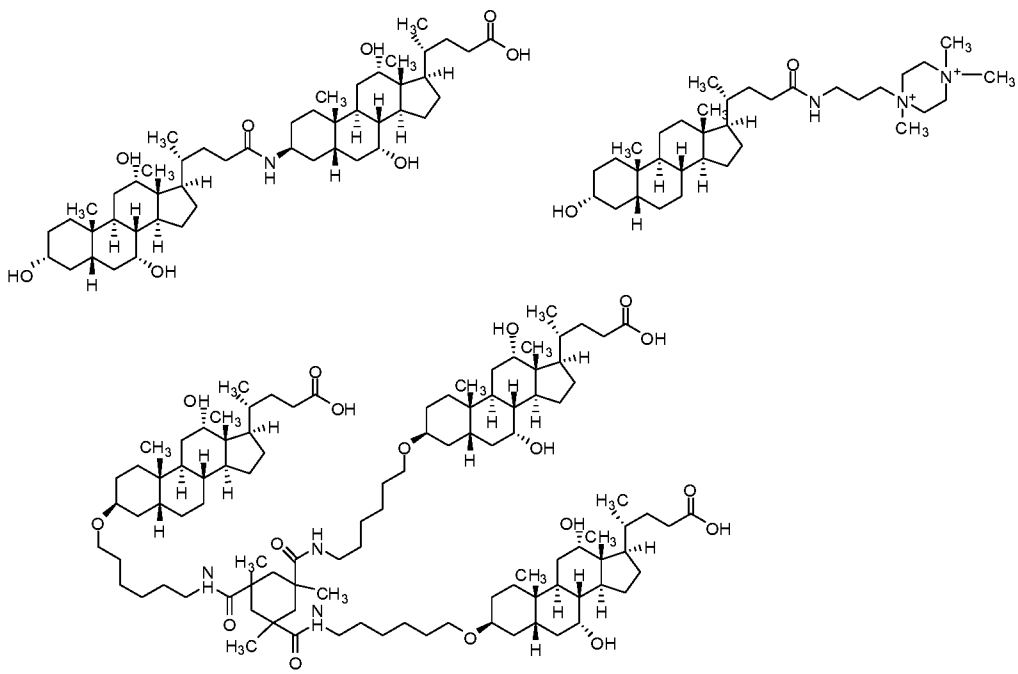
[00572] In certain embodiments, compounds that inhibit ASBT or any recuperative bile acid transporters are compounds that are described in EP1810689, US Patent Nos. 6,458,851, 7413536, 7514421, US Appl. Publication Nos. 2002/0147184, 2003/0119809, 2003/0149010, 2004/0014806, 2004/0092500, 2004/0180861, 2004/0180860, 2005/0031651, 2006/0069080, 2006/0199797, 2006/0241121, 2007/0065428, 2007/0066644, 2007/0161578, 2007/0197628, 2007/0203183, 2007/0254952, 2008/0070888, 2008/0070892, 2008/0070889, 2008/0070984, 2008/0089858, 2008/0096921, 2008/0161400, 2008/0167356, 2008/0194598, 2008/0255202, 2008/0261990, WO 2002/50027, WO2005/046797, WO2006/017257, WO2006/105913, WO2006/105912, WO2006/116499, WO2006/117076, WO2006/121861, WO2006/122186, WO2006/124713, WO2007/050628, WO2007/101531, WO2007/134862, WO2007/140934, WO2007/140894, WO2008/028590, WO2008/033431, WO2008/033464, WO2008/031501, WO2008/031500, WO2008/033465, WO2008/034534, WO2008/039829, WO2008/064788, WO2008/064789, WO2008/088836, WO2008/104306, WO2008/124505, and WO2008/130616; the compounds described therein that inhibit recuperative bile acid transport are hereby incorporated herein by reference.

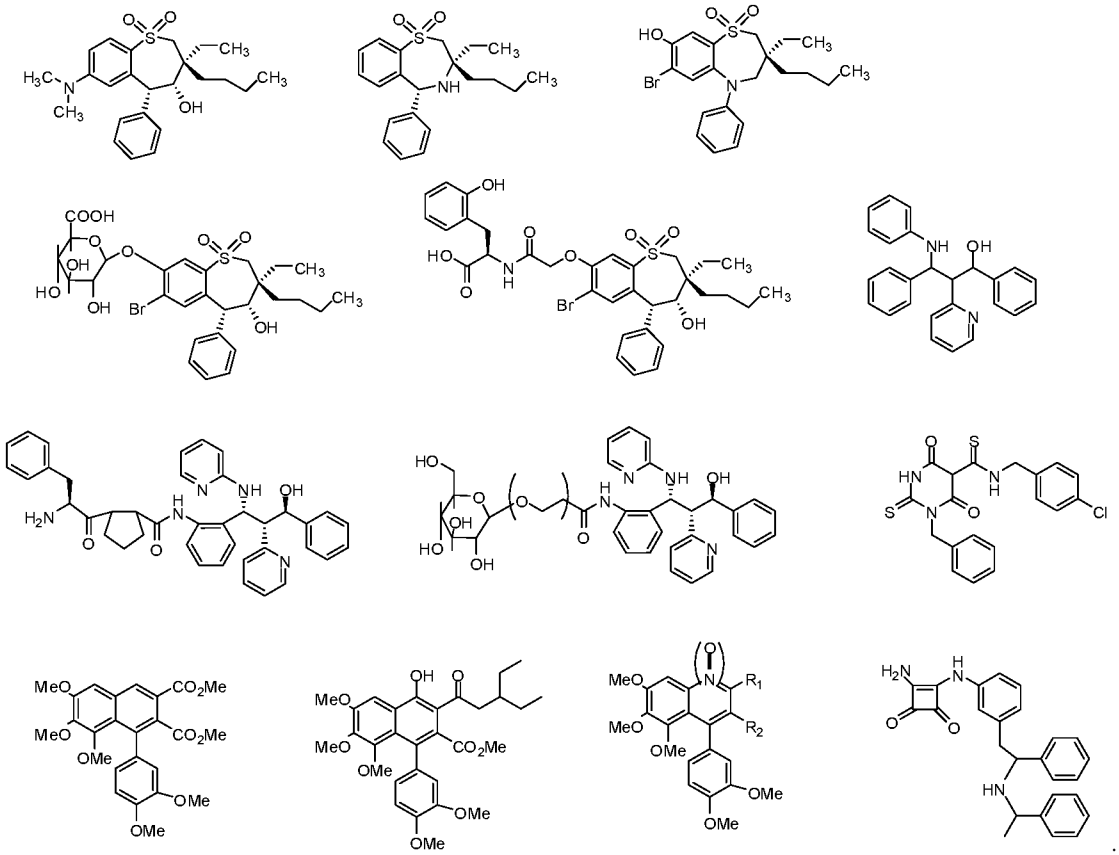
[00573] In certain embodiments, compounds that inhibit ASBT or any recuperative bile acid transporters are compounds described in WO93/16055, WO94/18183, WO94/18184, WO96/05188, WO96/08484, WO96/16051, WO97/33882, WO98/38182, WO99/35135, WO98/40375, WO99/64409, WO99/64410, WO00/01687, WO00/47568, WO00/61568, DE 19825804, WO00/38725, WO00/38726, WO00/38727 (including those compounds with a 2,3,4,5-tetrahydro-1-benzothiepine 1,1-dioxide structure), WO00/38728, WO01/66533, WO02/50051, EP0864582 (e.g. (3R,5R)-3-butyl-3-ethyl-1,1-dioxido-5-Phenyl-2,3,4,5-tetrahydro-1,4-benzo- thiazepin-8-yl (β-D-glucopyranosiduronic acid, WO94/24087, WO98/07749, WO98/56757, WO99/32478, WO99/35135, WO00/20392, WO00/20393, WO00/20410, WO00/20437, WO01/34570, WO00/35889, WO01/68637, WO01/68096, WO02/08211, WO03/020710, WO03/022825, WO03/022830, WO03/0222861, JP10072371, U.S. Patent. Nos. 5,910,494; 5,723,458; 5,817,652; 5,663,165; 5,998,400; 6,465,451, 5,994,391; 6,107,494; 6,387,924; 6,784,201; 6,875,877; 6,740,663; 6,852,753; 5,070,103,

6,114,322, 6,020,330, 7,179,792, EP251315, EP417725, EP489-423, EP549967, EP573848, EP624593, EP624594, EP624595, EP869121, EP1070703, WO04/005247, compounds disclosed as having IBAT activity in Drugs of the Future, 24, 425-430 (1999), Journal of Medicinal Chemistry, 48, 5837-5852, (2005) and Current Medicinal Chemistry, 13, 997-1016, (2006); the compounds described therein that inhibit recuperative bile acid transport are hereby incorporated herein by reference.

[00574] In some embodiments, compounds that inhibit ASBT or any recuperative bile acid transporter are benzothiepines, benzothiazepines (including 1,2-benzothiazepines; 1,4-benzothiazepines; 1,5-benzothiazepines; and/or 1,2,5-benzothiadiazepines). In some embodiments, compounds that inhibit ASBT or any recuperative bile acid transporter include and are not limited to S-8921 (disclosed in EP597107, WO 93/08155), 264W94 (GSK) disclosed in WO 96/05188; SC-435 (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 methanesulfonate salt), SC-635 (Searle); 2164U90 (3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide); BARI-1741 (Aventis SA), AZD 7508 (Astra Zeneca); barixibat (11-(D-gluconamido)-N-{2-[(1S,2R,3S)-3-hydroxy-3-phenyl-2-(2-pyridyl)-1-(2-pyridylamino)propyl]phenyl}undecanamide) or the like, or combinations thereof. In some embodiments, an ASBTI is:

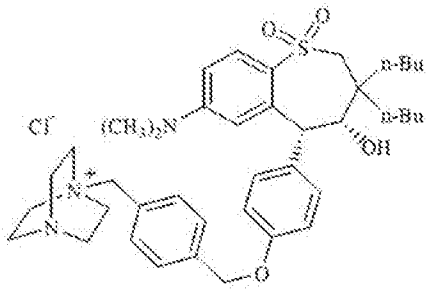
[00575]





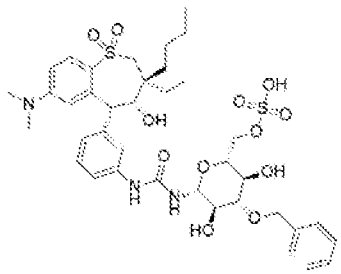
[00576] In certain embodiments, compounds described herein have one or more chiral centers. As such, all stereoisomers are envisioned herein. In various embodiments, compounds described herein are present in optically active or racemic forms. It is to be understood that the compounds of the present invention encompass racemic, optically-active, regioisomeric and stereoisomeric forms, or combinations thereof that possess the therapeutically useful properties described herein. Preparation of optically active forms is achieved in any suitable manner, including by way of non-limiting example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase. In some embodiments, mixtures of one or more isomer is utilized as the therapeutic compound described herein. In certain embodiments, compounds described herein contains one or more chiral centers. These compounds are prepared by any means, including enantioselective synthesis and/or separation of a mixture of enantiomers and/or diastereomers. Resolution of compounds and isomers thereof is achieved by any means including, by way of non-limiting example, chemical processes, enzymatic processes, fractional crystallization, distillation, chromatography, and the like.

[00577] In some embodiments, the ASBTI is



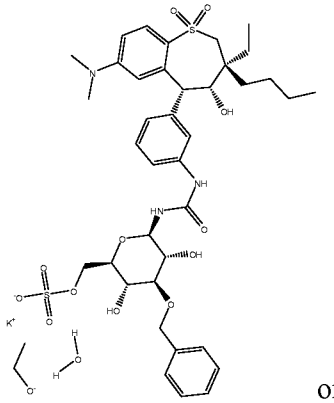
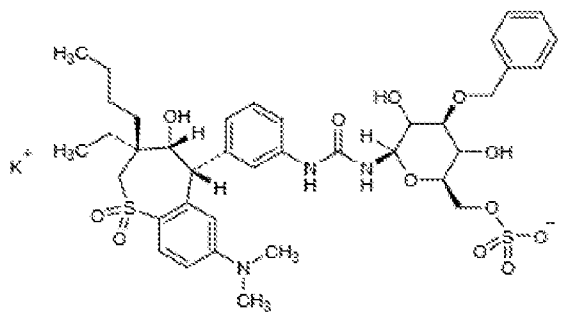
[00578] (maralixibat, LUM-001, SHP625, lopixibat chloride), or an alternative pharmaceutically acceptable salt thereof.

[00579] In some embodiments, the ASBTI is

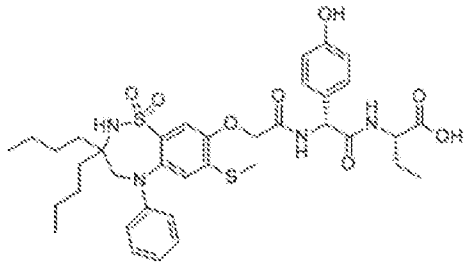


[00580] (volixibat, (2R,3R,4S,5R,6R)-4-benzyloxy-6-{3-[3-((3S,4R,5R)-3-butyl-7-dimethylamino-3-ethyl-4-hydroxy-1,1-dioxo-2,3,4,5-tetrahydro-1H-benzo[b]thiepin-5-yl)-phenyl]-ureido}-3,5-dihydroxy-tetrahydro-pyran-2-ylmethyl) hydrogen sulfate), or a pharmaceutically acceptable salt thereof.

[00581] In some embodiments, the ASBTI is

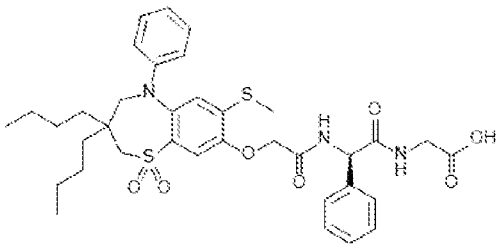
[00582]  or 

(LUM-002; SHP626; SAR548304; volixibat potassium), or an alternative pharmaceutically acceptable salt thereof.

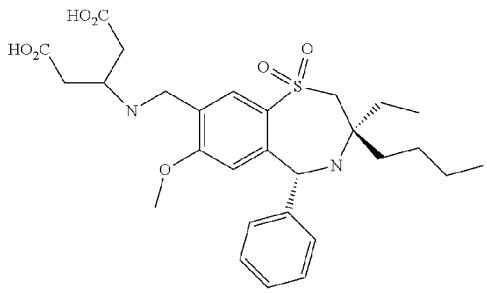


[00583] In various embodiments the ASBTI is (odevixibat; AZD8294; WHO10706; AR-H064974; SCHEMBL946468; A4250; 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-a-[N-((S)-1-carboxypropyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine), or a pharmaceutically acceptable salt thereof.

[00584] In some embodiments, the ASBTI is



(elobixibat; 2-[[(2R)-2-[[2-[(3,3-dibutyl-7-methylsulfanyl-1,1-dioxo-5-phenyl-2,4-dihydro-1λ6,5-benzothiazepin-8-yl)oxy]acetyl]amino]-2-phenylacetyl]amino]acetic acid), or a pharmaceutically acceptable salt thereof.



[00585] In some embodiments, the ASBTI is (GSK2330672; linerixibat; 3-((((3R,5R)-3-butyl-3-ethyl-7-(methyloxy)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,4-benzothiazepin-8-yl)methyl)amino)pentanedioic acid), or a pharmaceutically acceptable salt thereof.

[00586] In some embodiments, ASBTIs described herein are synthesized as described in, for example, WO 96/05188, U.S. Patent Nos. 5,994,391; 7,238,684; 6,906,058; 6,020,330; and 6,114,322.

[00587] In some embodiments, the ASBTI used in the methods or compositions of the present invention is maralixibat (SHP625), volixibat (SHP626), or odevixibat (A4250), or a pharmaceutically acceptable salt thereof.

[00588] In some embodiments, the ASBTI used in the methods or compositions of the present invention is maralixibat, or a pharmaceutically acceptable salt thereof.

[00589] In some embodiments, the ASBTI used in the methods or compositions of the present invention is volixibat, or a pharmaceutically acceptable salt thereof.

[00590] In some embodiments, the ASBTI used in the methods or compositions of the present invention is odevixibat, or a pharmaceutically acceptable salt thereof.

[00591] In some embodiments, the ASBTI used in the methods or compositions of the present invention is elobixibat, or a pharmaceutically acceptable salt thereof.

[00592] In some embodiments, the ASBTI used in the methods or compositions of the present invention is GSK2330672, or a pharmaceutically acceptable salt thereof.

[00593] In some embodiments, the ASBTI may comprise a mixture of different ASBTIs; for example, the ASBTI may be a composition comprising maralixibat, volixibat, odevixibat, GSK2330672, elobixibat, or various combinations thereof.

Methods

[00594] Provided herein is a method for treating or ameliorating cholestatic liver disease in a patient in need thereof, wherein the patient has a BSEP deficiency. The method comprises administering to the patient an Apical Sodium-dependent Bile Acid Transport Inhibitor (ASBTI).

[00595] In certain embodiments, the 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), BRIP 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. In some embodiments, the cholestatic liver disease is a pediatric form of liver disease.

[00596] In certain embodiments, a 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/or renal failure.

[00597] In some embodiments the patient has biliary atresia.

[00598] In some embodiments, the patient has intrahepatic cholestasis of pregnancy (ICP).

[00599] In certain embodiments, methods of the present invention comprise non-systemic administration of a therapeutically effective amount of an ASBTI. In certain embodiments, the methods comprise contacting the gastrointestinal tract, including the distal ileum and/or the colon and/or the rectum, of an individual in need thereof with an ASBTI. In various embodiments, the methods of the present invention cause a reduction in intraenterocyte bile acids, or a reduction in damage to hepatocellular or intestinal architecture caused by cholestasis or a cholestatic liver disease.

[00600] In various embodiments, methods of the present invention comprise delivering to ileum or colon of the individual a therapeutically effective amount of any ASBTI described herein.

[00601] In various embodiments the subject has a condition associated with, caused by or caused in part by a BSEP deficiency. In certain embodiments, the condition associated with, caused by or caused in part by the BSEP deficiency is neonatal hepatitis, primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), PFIC 2, benign recurrent intrahepatic cholestasis (BRIC), intrahepatic cholestasis of pregnancy (ICP), drug-induced cholestasis, oral-contraceptive-induced cholestasis, biliary atresia, or a combination thereof.

[00602] In various embodiments, methods of the present invention comprise reducing damage to hepatocellular or intestinal architecture or cells from cholestasis or a cholestatic liver disease comprising administration of a therapeutically effective amount of an ASBTI. In certain embodiments, the methods of the present invention comprise reducing intraenterocyte

bile acids/salts through administration of a therapeutically effective amount of an ASBTI to an individual in need thereof.

[00603] In some embodiments, methods of the present invention provide for inhibition of bile salt recycling upon administration of any of the compounds described herein to an individual. In some embodiments, an ASBTI described herein is systemically absorbed upon administration. In some embodiments, an ASBTI described herein is not absorbed systemically. In some embodiments, an ASBTI herein is administered to the individual orally. In some embodiments, an ASBTI described herein is delivered and/or released in the distal ileum of an individual.

[00604] In various embodiments, contacting the distal ileum of an individual with an ASBTI (e.g., any ASBTI described herein) inhibits bile acid reuptake and increases the concentration of bile acids/salts in the vicinity of L-cells in the distal ileum and/or colon and/or rectum, thereby reducing intraenterocyte bile acids, reducing serum and/or hepatic bile acid levels, reducing overall serum bile acid load, and/or reducing damage to ileal architecture caused by cholestasis or a cholestatic liver disease. Without being limited to any particular theory, reducing serum and/or hepatic bile acid levels ameliorates hypercholemia and/or cholestatic disease.

[00605] Administration of a compound described herein may be achieved in any suitable manner including, by way of non-limiting example, by oral, enteric, parenteral (e.g., intravenous, subcutaneous, intramuscular), intranasal, buccal, topical, rectal, or transdermal administration routes. Any compound or composition described herein may be administered in a method or formulation appropriate to treat a newborn or an infant. Any compound or composition described herein may be administered in an oral formulation (e.g., solid or liquid) to treat a newborn or an infant. Any compound or composition described herein may be administered prior to ingestion of food, with food or after ingestion of food.

[00606] In certain embodiments, a compound or a composition comprising a compound described herein is administered for prophylactic and/or therapeutic treatments. In therapeutic applications, the compositions are administered to an individual already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest the symptoms of the disease or condition. In various instances, amounts effective for this use depend on the severity and course of the disease or condition, previous therapy, the individual's health status, weight, and response to the drugs, and the judgment of the treating physician.

[00607] In prophylactic applications, compounds or compositions containing compounds described herein may be administered to an individual susceptible to or otherwise at risk of a particular disease, disorder or condition. In certain embodiments of this use, the precise amounts of compound administered depend on the individual's state of health, weight, and the like. Furthermore, in some instances, when a compound or composition described herein is administered to an individual, effective amounts for this use depend on the severity and course of the disease, disorder or condition, previous therapy, the individual's health status and response to the drugs, and the judgment of the treating physician.

[00608] In certain embodiments of the methods of the present invention, wherein following administration of a selected dose of a compound or composition described herein, an individual's condition does not improve, upon the doctor's discretion the administration of a compound or composition described herein is optionally administered chronically, that is, for an extended period of time, including throughout the duration of the individual's life in order to ameliorate or otherwise control or limit the symptoms of the individual's disorder, disease or condition.

[00609] In certain embodiments of the methods of the present invention, an effective amount of a given agent varies depending upon one or more of a number of factors such as the particular compound, disease or condition and its severity, the identity (e.g., weight) of the subject or host in need of treatment, and is determined according to the particular circumstances surrounding the case, including, e.g., the specific agent being administered, the route of administration, the condition being treated, and the subject or host being treated. In some embodiments, doses administered include those up to the maximum tolerable dose. In some embodiments, doses administered include those up to the maximum tolerable dose by a newborn or an infant.

[00610] In various embodiments of the methods of the present invention, a desired dose is conveniently presented in a single dose or in divided doses administered simultaneously (or over a short period of time) or at appropriate intervals, for example as two, three, four or more sub-doses per day. In various embodiments, a single dose of an ASBTI is administered every 6 hours, every 12 hours, every 24 hours, every 48 hours, every 72 hours, every 96 hours, every 5 days, every 6 days, or once a week. In some embodiments the total single dose of an ASBTI is in a range described below.

[00611] In various embodiments of methods of the present invention, in the case wherein the patient's status does improve, upon the doctor's discretion an ASBTI is optionally given

continuously; alternatively, the dose of drug being administered is temporarily reduced or temporarily suspended for a certain length of time (i.e., a "drug holiday"). The length of the drug holiday optionally varies between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, or 365 days. The dose reduction during a drug holiday includes from 10%-100% of the original dose, including, by way of example only, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of the original dose. In some embodiments the total single dose of an ASBTI is in a range described below.

[00612] Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, the dosage or the frequency of administration, or both, is reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained. In some embodiments, patients require intermittent treatment on a long-term basis upon any recurrence of symptoms.

[00613] In certain instances, there are a large number of variables in regard to an individual treatment regime, and considerable excursions from these recommended values are considered within the scope described herein. Dosages described herein are optionally altered depending on a number of variables such as, by way of non-limiting example, the activity of the compound used, the disease or condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the disease or condition being treated, and the judgment of the practitioner.

[00614] Toxicity and therapeutic efficacy of such therapeutic regimens are optionally determined by pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, the determination of the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD_{50} and ED_{50}. Compounds exhibiting high therapeutic indices are prefer ed. In certain embodiments, data obtained from cell culture assays and animal studies are used in formulating a range of dosage for use in human. In specific embodiments, the dosage of compounds described herein lies within a range of circulating concentrations that include the ED_{50} with minimal toxicity. The dosage optionally varies within this range depending upon the dosage form employed and the route of administration utilized.

[00615] In certain embodiments, the composition used or administered comprises an absorption inhibitor, a carrier, and one or more of a cholesterol absorption inhibitor, an enteroendocrine peptide, a peptidase inhibitor, a spreading agent, and a wetting agent.

[00616] In some embodiments of methods of the present invention, the composition used to prepare an oral dosage form or administered orally comprises an absorption inhibitor, an orally suitable carrier, an optional cholesterol absorption inhibitor, an optional enteroendocrine peptide, an optional peptidase inhibitor, an optional spreading agent, and an optional wetting agent. In certain embodiments, the orally administered compositions evoke an anorectal response. In specific embodiments, the anorectal response is an increase in secretion of one or more enteroendocrine by cells in the colon and/or rectum (e.g., in L-cells the epithelial layer of the colon, ileum, rectum, or a combination thereof). In some embodiments, the anorectal response persists for at least 1, 2, 3, 4 ,5 ,6 ,7 ,8, 9, 10, 11,12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24 hours. In other embodiments the anorectal response persists for a period between 24 hours and 48 hours, while in other embodiments the anorectal response persists for persists for a period greater than 48 hours.

Genotyping

[00617] In various embodiments, the BSEP deficiency is progressive familial intrahepatic cholestasis (PFIC 2), benign recurrent intrahepatic cholestasis, or intrahepatic cholestasis of pregnancy. In various embodiments the patient has residual BSEP function. In various embodiments, the patient has at least about 95%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20%, 25%, 20%, 5%, 2.5%, or 1% BSEP function relative to a healthy individual without any cholestatic liver disease. In various embodiments, the patent has a maximum of about 99%, 95%, 95%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20%, 25%, 20%, 5%, or 2.5% BSEP function relative to a healthy individual without any cholestatic liver disease. The BSEP deficiency can result in impaired or reduced bile flow or cholestasis.

[00618] In various embodiments, the BSEP deficiency is caused by a mutation in an *ABCB11* gene. In various embodiments, the mutation in the *ABCB11* gene is a non-truncating mutation. In general, truncating mutations to the *ABCB11* gene can result in lack of residual function of the encoded BSEP ("severe" mutation). In various embodiments, the *ABCB11* gene includes a mutation and does not comprise any truncating mutations. The *ABCB11* gene mutation can be a missense or nonsense mutation, an insertion, or a deletion. In some

embodiments, the *ABCB11* gene includes an E297G or a D482G mutation, alternatively referred to as "mild" mutations or "mild PFIC 2." In some embodiments, the *ABCB11* gene comprises a missense mutation and does not include an E297G or a D482G missense mutation, alternatively referred to as "moderate" mutations or "moderate PFIC 2." The *ABCB11* gene can include an E297G, D482G, alternative missense mutations, insertions, deletions, and various combinations thereof. In various embodiments, the alternative missense mutation may be selected from one of those mutations listed in Byrne, et al., "Missense Mutations and Single Nucleotide Polymorphisms in *ABCB11* Impair Bile Salt Export Pump Processing and Function or Disrupt Pre-Messanger RNA Splicing," *Hepatology*, 49:553-567 (2009), which is incorporated herein by reference in its entirety for all purposes.

[00619] In various embodiments, the patient has total loss of BSEP activity. In various embodiments, the patient having total loss of BSEP activity is homozygous for *ABCB11* genes having mutations resulting in total loss of encoded BSEP activity (e.g., truncating or frame-shift mutations). In various embodiments, the patient has residual BSEP activity. In various embodiments, the patient having residual BSEP activity is heterozygous for an *ABCB11* gene having mutations resulting in total loss of encoded BSEP activity (e.g., patients having an *ABCB11* gene with a truncating mutation and a wild type *ABCB11* gene or patients having having an *ABCB11* gene with a truncating mutation and and *ABCB11* gene having mutations encoding BSEP having residual activity but activity that is reduced relative to wild type BSEP). In certain emgodiments, the patient having residual BSEP activity is homozygous for *ABCB11* genes having mutations resulting in residual BSEP activity and reduced activity of BSEP relative to wild type (e.g., patients having *ABCB11* genes with the same or different missense mutation(s)). In some embodiments, the patient having residual BSEP activity is heterozygous for *ABCB11* genes having mutations resulting in residual BSEP activity and reduced activity of BSEP relative to wild type (e.g., patients having a wild type *ABCB11* gene and an *ABCB11* gene having a missense mutation).

[00620] In various embodiments, the method includes determining a genotype of the patient. Determining the genotype can include any of various methods known in the art for determining a gene sequence for the patient, including as non-limiting examples restriction fragment length polymorphism identification of genomic DNA, random amplified polymorphic detection of genomic DNA, amplified fragment length polymorphism detection, polymerase chain reaction, DNA sequencing, allele specific oligonucleotide probes,

hybridization to DNA microarrays or beads, and various combinations thereof. In various embodiments, determining the genotype includes determining a sequence of the *ABCB11* gene.

[00621] In some embodiments, the method includes determining the genotype includes identifying and characterizing a mutation in the *ABCB11* gene. Determining the genotype can include determining a sequence for a portion or an entirety of the *ABCB11* gene. Determining the genotype can further include determining a sequence for a genomic region surrounding the *ABCB11* gene or determining a sequence for one or more introns and/or exons of the *ABCB11* gene. Determining the genotype can include characterizing the *ABCB11* gene by identifying one, multiple, or all mutations of *ABCB11* gene-encoding alleles of the patient. In various embodiments, determining the genotype includes determining whether or not the *ABCB11* gene has a truncating mutation, an insertion, a deletion, a missense mutation, the E297G mutation, the D482G mutation, a splice site mutation, a nonsense mutation, a frameshift mutation, or various combinations thereof.

Dosages

[00622] In various embodiments, the patient is a pediatric patient under the age of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 years old. In certain embodiments, the pediatric patient is a newborn, a pre-term newborn, an infant, a toddler, a preschooler, a school-age child, a pre-pubescent child, post-pubescent child, an adolescent, or a teenager under the age of eighteen. In some embodiments, the pediatric patient is a newborn, a pre-term newborn, an infant, a toddler, a preschooler, or a school-age child. In some embodiments, the pediatric patient is a newborn, a pre-term newborn, an infant, a toddler, or a preschooler. In some embodiments, the pediatric patient is a newborn, a pre-term newborn, an infant, or a toddler. In some embodiments, the pediatric patient is a newborn, a pre-term newborn, or an infant. In some embodiments, the pediatric patient is a newborn. In some embodiments, the pediatric patient is an infant. In some embodiments, the pediatric patient is a toddler.

[00623] In some embodiments, the patient is an adult over the age of 18, 20, 30, 40, 50, 60, or 70.

[00624] In various embodiments the ASBTI is maralixibat, volixibat, odevixibat, or a pharmaceutically acceptable salt thereof.

[00625] In various embodiments, efficacy and safety of ASBTI administration to the patient is monitored by measuring serum levels of 7α-hydroxy-4-cholesten-3-one (7αC4), sBA

concentration, a ratio of 7αC4 to sBA (7αC4:sBA), serum bilirubin concentration, serum ALT concentration, serum AST concentration, or a combination thereof. In various embodiments, efficacy of ASBTI administration is measured by monitoring observer-reported itch reported outcome (ITCHRO(OBS)) score, a HRQoL (e.g., PedsQL) score, a CSS score, a height Z-score, a weight Z-score, or various combinations thereof. In various embodiments, the method includes monitoring serum levels of 7α-hydroxy-4-cholesten-3-one (7αC4), sBA concentration, a ratio of 7αC4 to sBA (7αC4:sBA), serum bilirubin concentration, serum ALT concentration, serum AST concentration, or a combination thereof. In various embodiments, the method includes monitoring observer-reported itch reported outcome (ITCHRO(OBS)) score, a HRQoL (e.g., PedsQL) score, a CSS score, a height Z-score, a weight Z-score or various combinations thereof.

[00626] In some embodiments, the ASBTI is administered at a dose of about or at least about 0.5 μg/kg, 1 μg/kg, 2 μg/kg, 3 μg/kg, 4 μg/kg, 5 μg/kg, 6 μg/kg, 7 μg/kg, 8 μg/kg, 9 μg/kg, 10 μg/kg, 15 μg/kg, 20 μg/kg, 25 μg/kg, 30 μg/kg, 35 μg/kg, 40 μg/kg, 45 μg/kg, 50 μg/kg, 55 μg/kg, 60 μg/kg, 65 μg/kg, 70 μg/kg, 75 μg/kg, 80 μg/kg, 85 μg/kg, 90 μg/kg, 100 μg/kg, 140 μg/kg, 150 μg/kg, 200 μg/kg, 240 μg/kg, 280 μg/kg, 300 μg/kg, 250 μg/kg, 280 μg/kg, 300 μg/kg, 400 μg/kg, 500 μg/kg, 560 μg/kg, 600 μg/kg, 700 μg/kg, 800 μg/kg, 900 μg/kg, 1,000 μg/kg, 1,100 μg/kg, 1,200 μg/kg, 1,300 μg/kg, 1,400 μg/kg, 1500 μg/kg, 1,600 μg/kg, 1,700 μg/kg, 1,800 μg/kg, 1,900 μg/kg, or 2,000 μg/kg. In various embodiments, the ASBTI is administered at a dose not exceeding about 1 μg/kg, 2 μg/kg, 3 μg/kg, 4 μg/kg, 5 μg/kg, 6 μg/kg, 7 μg/kg, 8 μg/kg, 9 μg/kg, 10 μg/kg, 15 μg/kg, 20 μg/kg, 25 μg/kg, 30 μg/kg, 35 μg/kg, 40 μg/kg, 45 μg/kg, 50 μg/kg, 55 μg/kg, 60 μg/kg, 65 μg/kg, 70 μg/kg, 75 μg/kg, 80 μg/kg, 85 μg/kg, 90 μg/kg, 100 μg/kg, 140 μg/kg, 150 μg/kg, 200 μg/kg, 240 μg/kg, 280 μg/kg, 300 μg/kg, 250 μg/kg, 280 μg/kg, 300 μg/kg, 400 μg/kg, 500 μg/kg, 560 μg/kg, 600 μg/kg, 700 μg/kg, 800 μg/kg, 900 μg/kg, 1,000 μg/kg, 1,100 μg/kg, 1,200 μg/kg, 1,300 μg/kg, 1,400 μg/kg, 1,500 μg/kg, 1,600 μg/kg, 1,700 μg/kg, 1,800 μg/kg, 1,900 μg/kg, 2,000, or 2,100 μg/kg. In various embodiments, the ASBTI is administered at a dose of about or of at least about 0.5 mg/day, 1 mg/day, 2 mg/day, 3 mg/day, 4 mg/day, 5 mg/day, 6 mg/day, 7 mg/day, 8 mg/day, 9 mg/day, 10 mg/day, 11 mg/day, 12 mg/day, 13 mg/day, 14 mg/day, 15 mg/day, 16 mg/day, 17 mg/day, 18 mg/day, 19 mg/day, 20 mg/day, 30 mg/day, 40 mg/day, 50 mg/day, 60 mg/day, 70 mg/day, 80 mg/day, 90 mg/day, 100 mg/day, 150 mg/day, 200 mg/day, 300 mg/day, 500 mg/day, 600 mg/day, 700 mg/day, 800 mg/day, 900 mg/day, 1000 mg/day. In various embodiments, the ASBTI is administered at a dose of not more than about

1 mg/day, 2 mg/day, 3 mg/day, 4 mg/day, 5 mg/day, 6 mg/day, 7 mg/day, 8 mg/day, 9 mg/day, 10 mg/day, 11 mg/day, 12 mg/day, 13 mg/day, 14 mg/day, 15 mg/day, 16 mg/day, 17 mg/day, 18 mg/day, 19 mg/day, 20 mg/day, 30 mg/day, 40 mg/day, 50 mg/day, 60 mg/day, 70 mg/day, 80 mg/day, 90 mg/day, 100 mg/day, 150 mg/day, 200 mg/day, 300 mg/day, 500 mg/day, 600 mg/day, 700 mg/day, 800 mg/day, 900 mg/day, 1,000 mg/day, 1,100 mg/day.

[00627] In some embodiments, the ASBTI is administered at a dose of from about 140 μg/kg/day to about 1400 μg/kg/day. In various embodiments, the ASBTI is administered at a dose of about or at least about 0.5 μg/kg/day, 1 μg/kg/day, 2 μg/kg/day, 3 μg/kg/day, 4 μg/kg/day, 5 μg/kg/day, 6 μg/kg/day, 7 μg/kg/day, 8 μg/kg/day, 9 μg/kg/day 10 μg/kg/day, 15 μg/kg/day, 20 μg/kg/day, 25 μg/kg/day, 30 μg/kg/day, 35 μg/kg/day, 40 μg/kg/day, 45 μg/kg/day, 50 μg/kg/day, 100 μg/kg/day, 140 μg/kg/day, 150 μg/kg/day, 200 μg/kg/day, 240 μg/kg/day, 280 μg/kg/day, 300 μg/kg/day, 250 μg/kg/day, 280 μg/kg/day, 300 μg/kg/day, 400 μg/kg/day, 500 μg/kg/day, 560 μg/kg/day, 600 μg/kg/day, 700 μg/kg/day, 800 μg/kg/day, 900 μg/kg/day, 1,000 μg/kg/day, 1,100 μg/kg/day, 1,200 μg/kg/day, or 1,300 μg/kg/day. In various embodiments, the ASBTI is administered at a dose not exceeding about 1 μg/kg/day, 2 μg/kg/day, 3 μg/kg/day, 4 μg/kg/day, 5 μg/kg/day, 6 μg/kg/day, 7 μg/kg/day, 8 μg/kg/day, 9 μg/kg/day 10 μg/kg/day, 15 μg/kg/day, 20 μg/kg/day, 25 μg/kg/day, 30 μg/kg/day, 35 μg/kg/day, 40 μg/kg/day, 45 μg/kg/day, 50 μg/kg/day, 100 μg/kg/day, 140 μg/kg/day, 150 μg/kg/day, 200 μg/kg/day, 240 μg/kg/day, 280 μg/kg/day, 300 μg/kg/day, 250 μg/kg/day, 280 μg/kg/day, 300 μg/kg/day, 400 μg/kg/day, 500 μg/kg/day, 560 μg/kg/day, 600 μg/kg/day, 700 μg/kg/day, 800 μg/kg/day, 900 μg/kg/day, 1,000 μg/kg/day, 1,100 μg/kg/day, 1,200 μg/kg/day, 1,300 μg/kg/day, or 1,400 μg/kg/day. In various embodiments, the ASBTI is administered at a dose of from about 0.5 μg/kg/day to about 500 μg/kg/day, from about 0.5 μg/kg/day to about 250 μg/kg/day, from about 1 μg/kg/day to about 100 μg/kg/day, from about 10 μg/kg/day to about 50 μg/kg/day, from about 10 μg/kg/day to about 100 μg/kg/day, from about 0.5 μg/kg/day to about 2000 μg/kg/day, from about 280 μg/kg/day to about 1400 μg/kg/day, from about 420 μg/kg/day to about 1400 μg/kg/day, from about 250 to about 550 μg/kg/day, from about 560 μg/kg/day to about 1400 μg/kg/day, from 700 μg/kg/day to about 1400 μg/kg/day, from about 560 μg/kg/day to about 1200 μg/kg/day, from about 700 μg/kg/day to about 1200 μg/kg/day, from about 560 μg/kg/day to about 1000 μg/kg/day, from about 700 μg/kg/day to about 1000 μg/kg/day, from about 800 μg/kg/day to about 1000 μg/kg/day, from about 200 μg/kg/day to about 600

μg/kg/day, from about 300 μg/kg/day to about 600 μg/kg/day, from about 400 μg/kg/day to about 500 μg/kg/day, from about 400 μg/kg/day to about 600 μg/kg/day, from about 400 μg/kg/day to about 700 μg/kg/day, from about 400 μg/kg/day to about 800 μg/kg/day, from about 500 μg/kg/day to about 800 μg/kg/day, from about 500 μg/kg/day to about 900 μg/kg/day, from about 600 μg/kg/day to about 900 μg/kg/day, from about 700 μg/kg/day to about 900 μg/kg/day, from about 200 μg/kg/day to about 600 μg/kg/day, from about 800 μg/kg/day to about 900 μg/kg/day, from about 100 μg/kg/day to about 1500 μg/kg/day, from about 300 μg/kg/day to about 2,000 μg/kg/day, or from about 400 μg/kg/day to about 2000 μg/kg/day.

[00628] In some embodiments, the ASBTI is administered at a dose of from about 30 μg/kg to about 1400 μg/kg per dose. In some embodiments, the ASBTI is administered at a dose of from about 0.5 μg/kg to about 2000 μg/kg per dose, from about 0.5 μg/kg to about 1500 μg/kg per dose, from about 100 μg/kg to about 700 μg/kg per dose, from about 5 μg/kg to about 100 μg/kg per dose, from about 10 μg/kg to about 500 μg/kg per dose, from about 50 μg/kg to about 1400 μg/kg per dose, from about 300 μg/kg to about 2,000 μg/kg per dose, from about 60 μg/kg to about 1200 μg/kg per dose, from about 70 μg/kg to about 1000 μg/kg per dose, from about 70 μg/kg to about 700 μg/kg per dose, from 80 μg/kg to about 1000 μg/kg per dose, from 80 μg/kg to about 800 μg/kg per dose, from 100 μg/kg to about 800 μg/kg per dose, from 100 μg/kg to about 600 μg/kg per dose, from 150 μg/kg to about 700 μg/kg per dose, from 150 μg/kg to about 500 μg/kg per dose, from 200 μg/kg to about 400 μg/kg per dose, from 200 μg/kg to about 300 μg/kg per dose, or from 300 μg/kg to about 400 μg/kg per dose.

[00629] In some embodiments, the ASBTI is administered at a dose of from about 0.5 mg/day to about 550 mg/day. In various embodiments, the ASBTI is administered at a dose of from about 1 mg/day to about 500 mg/day, from about 1 mg/day to about 300 mg/day , from about 1 mg/day to about 200 mg/day, from about 2 mg/day to about 300 mg/day, from about 2 mg/day to about 200 mg/day, from about 4 mg/day to about 300 mg/day, from about 4 mg/day to about 200 mg/day, from about 4 mg/day to about 150 mg/day, from about 5 mg/day to about 150 mg/day, from about 5 mg/day to about 100 mg/day, from about 5 mg/day to about 80 mg/day, from about 5 mg/day to about 50 mg/day, from about 5 mg/day to about 40 mg/day, from about 5 mg/day to about 30 mg/day, from about 5 mg/day to about 20 mg/day, from about 5 mg/day to about 15 mg/day, from about 10 mg/day to about 100 mg/day, from about 10 mg/day to about 80 mg/day, from about 10 mg/day to about 50

mg/day, from about 10 mg/day to about 40 mg/day, from about 10 mg/day to about 20 mg/day, from about 20 mg/day to about 100 mg/day, from about 20 mg/day to about 80 mg/day, from about 20 mg/day to about 50 mg/day, or from about 20 mg/day to about 40 mg/day, or from about 20 mg/day to about 30 mg/day.

[00630] In various embodiments, the dose of the ASBTI is a first dose level. In various embodiments, the dose of the ASBTI is a second dose level. In some embodiments, the second dose level is greater than the first dose level. In some embodiments, the second dose level is about or at least about 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90 or 100 times or fold greater than the first dose level. In some embodiments, the second dose level is not in excess of about 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100, or 150 times or fold greater than the first dose level.

[00631] In various embodiments, the ASBTI is administered once daily (QD) at one of the above doses or within one of the above dose ranges. In various embodiments, the ASBTI is administered twice daily (BID) at one of the above doses or within one of the above dose ranges. In various embodiments, an ASBTI dose is administered daily, every other day, twice a week, or once a week.

[00632] In various embodiments, the ASBTI is administered regularly for a period of about or of at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 48, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 600, 700, or 800 weeks. In various embodiments, the ASBTI is administered for not more than about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 48, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 600, 700, 800, or 1000 weeks. In various embodiments, the ASBTI is administered regularly for a period of about or of at least about 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, or 10 years. In various embodiments, the ASBTI is administered regularly for a period not in excess of about 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 15 years.

Dose Modulation

[00633] In various embodiments, the method includes modulating a dosage of the ASBTI administered to the patient. The modulation includes determining the 7αC4:sBA ratio for the patient at a baseline (e.g., prior to administration of the ASBTI or prior to modulating (e.g., increasing) a dosage of the ASBTI), and further determining the 7αC4:sBA ratio after administering the ASBTI at a first dose or modulating (e.g., increasing) a dosage amount of the ASBTI to a second dose. If the 7αC4:sBA ratio does not increase by at least 1, 1.25, 1.5,

1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 50, 75, 100, 150, 200, 300, 500, 750, 1,000, 2,000, 3,000, 4,000, 5,000 or 10,000-fold from baseline, the dose of the ASBTI is increased until the ratio increases at least about 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 50, 75, 100, 150, 200, 300, 500, 750, 1,000, 2,000, 3,000, 4,000, 5,000 or 10,000-fold relative to baseline. In various embodiments, the dose of the ASBTI is increased or decreased to achieve and maintain a particular 7αC4:sBA ratio.

[00634] In various embodiments, the modulating includes increasing a dose of the ASBTI from a first dose level to a second dose level greater than the first dose level if the 7αC4:sBA ratio initially increases by at least 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 50, 75, 100, 150, 200, 300, 500, 750, 1,000, 2,000, 3,000, 4,000, 5,000 or 10,000-fold from baseline and then begins to decrease or decreases to less than 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 50, 75, 100, 150, 200, 300, 500, 750, 1,000, 2,000, 3,000, 4,000, 5,000 or 10,000-fold or greater higher than baseline. The dose level is increased until the 7αC4:sBA ratio increases to at least 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 50, 75, 100, 150, 200, 300, 500, 750, 1,000, 2,000, 3,000, 4,000, 5,000 or 10,000-fold from the baseline.

[00635] In some embodiments, the modulation includes administering a first dose of the ASBTI to the patient. If the 7αC4:sBA ratio does not increase or increase by at least 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 50, 75, 100, 150, 200, 300, 500, 750, 1,000, 2,000, 3,000, 4,000, 5,000 or 10,000-fold fold from baseline, the patient is then administered a second dose of the ASBTI higher than the first dose. The dose administered to the patient continues to be increased until the 7αC4:sBA ratio increases by at least 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 50, 75, 100, 150, 200, 300, 500, 750, 1,000, 2,000, 3,000, 4,000, 5,000 or 10,000-fold from baseline.

[00636] In various embodiments, the 7αC4:sBA ratio is measured about daily, bi-weekly, weekly, bi-monthly, monthly, every two months, every three months, every four months, every five months, every six months, or annually, and the dose of the ASBTI is modulated as necessary each time the ratio is measured.

Predicting patient response based upon genotype

[00637] In an aspect of the invention, a prediction method is provided for predicting patient response to treatment of a cholestatic liver disease. The treatment includes administering to the patient in need of such treatment an ASBTI. The method includes determining the

genotype of the patient, as described above, and predicting patient response to the treatment based upon the genotype. In various embodiments, the patient has a BSEP deficiency. In some embodiments, the patient has PFIC 2.

[00638] In various embodiments the prediction method includes predicting that the patient will not be responsive to administration of the ASBTI if the *ABCB11* gene comprises a truncating mutation. In some embodiments, the method includes predicting that the patient will not be responsive to administration of the ASBTI if the *ABCB11* gene comprises a mutation that leads to a lack of any residual BSEP activity in the patient (i.e., to a total loss of BSEP activity). In some embodiments, the method includes predicting that the patient will not be responsive to administration of the ASBTI if the patient has a genotype that corresponds to total lack or loss of BSEP activity (e.g., the patient has a genome sequence that includes no non-truncated alleles of the *ABCB11* gene). In various embodiments, the prediction method includes predicting that the patient will be responsive to administration of the ASBTI if the *ABCB11* gene comprises mutations that result in residual BSEP activity and the *ABCB11* gene comprises no mutations that result in absence of BSEP activity. One of skill in the art will understand that if the patient has a genome including at least one functional *ABCB11* gene, the patient will have residual BSEP activity.

[00639] In some embodiments, the prediction method includes predicting that if the *ABCB11* gene comprises the E297G mutation or the D482G mutation the method further comprises predicting that the patient will be responsive to administration of the ASBTI at the first daily dose. Further, if the *ABCB11* gene comprises an alternative missense mutation and not the E287G or the D482G mutation, the method further includes predicting that the patient will be responsive to administration of the ASBTI at the second daily dose, where the second daily dose is greater than the first daily dose. If the patient is predicted to be responsive to administration of the ASBTI, the method further includes administering the ASBTI to the patient at the first daily dose or the second daily dose. In various embodiments, the ASBTI is not administered to the patient if the patient is predicted to not respond to ASBTI treatment.

Method of treatment using genotype information

[00640] In an aspect of the invention, a method is provided for treating or ameliorating cholestatic liver disease in a patient in need thereof, where the patient has a BSEP deficiency. The method includes determining a genotype of the patient, as described above. The method also includes using the genotype of the patient to predict whether the patient will be or will

not be responsive to treatment with the ASBTI, as described above. The method further includes administering the ASBTI to the patient if the patient is predicted to be responsive to administration of the ASBTI. In various embodiments, the BSEP deficiency is PFIC2.

[00641] In various embodiments, the method of the invention includes following a first dosing regimen of the ASBTI if the *ABCB11* gene comprises an E297G or D482G mutation and following a second dosing regimen of the ASBTI if the *ABCB11* gene comprises a missense mutation and does not comprise the E297G or the D482G mutation. In some embodiments, the first dosing regimen comprises administering a first daily dose of the ASBTI and the second dosing regimen comprises administering a second total daily dose of the ASBTI, where the first total daily dose is greater than the second total daily dose.

[00642] In various embodiments, the first dosing regimen is not equivalent to the second dosing regimen in terms of administration frequency, dose, or a combination thereof. The first dosing regimen and the second dosing regimen may include any of the various above listed dosing frequencies, administration of any of the various above listed dosage levels to the patient, and various combinations thereof.

Reduction in symptoms or change in disease-relevant laboratory measures of cholestatic liver disease

[00643] In various embodiments of the above methods of the invention, administration of the ASBTI results in a reduction in a symptom or change in a disease-relevant laboratory measure of the cholestatic liver disease (i.e., improvement in the patient's condition) that is maintained for about or for at least about 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, 24 weeks, 25 weeks, 26 weeks, 27 weeks, 28 weeks, 29 weeks, 30 weeks, 31 weeks, 32 weeks, 33 weeks, 34 weeks, 35 weeks, 36 weeks, 37 weeks, 38 weeks, 39 weeks, 40 weeks, 41 weeks, 42 weeks, 43 weeks, 44 weeks, 45 weeks, 46 weeks, 47 weeks, 48 weeks, 49 weeks, 50 weeks, 51 weeks, 52 weeks, 1 year, 13 months, 14 months, 15 months, 16 months, 17 months, 18 months, 19 months, 20 months, 21 months, 22 months, 23 months, 23 months, 2 years, 2.5 years, 3 years, 3.5 years, 4 years, 4.5 years, 5 years, 5.5 years, 6 years, 6.5 years, 7 years, 8 years, 9 years, or 10 years. In various embodiments, the reduction in the symptom or a change in a disease-relevant laboratory measure comprises a reduction in sBA concentration, an increase in serum 7αC4 concentration, an increase in the 7αC4:sBA ratio, an increase in fBA excretion, a reduction in

pruritis, a reduction in ALT levels, an increase in a quality of life inventory score, an increase in a quality of life inventory score related to fatigue, or a combination thereof. In various embodiments, the reduction in the symptom or a change in a disease-relevant laboratory measure is determined relative to a baseline level. That is, the reduction in the symptom or a change in a disease-relevant laboratory measure is determined relative to a measurement of the symptom or a change in a disease-relevant laboratory measure prior to 1) changing a dose level of the ASBTI administered to the patient, 2) changing a dosing regimen followed for the patient, 3) commencing administration of the ASBTI, or 4) any other of various alterations made with the intention of reducing the symptom or a change in a disease-relevant laboratory measure in the patient. In various embodiments, the reduction in symptom or a change in a disease-relevant laboratory measure is a statistically significant reduction.

[00644] In some embodiments, the patient is the pediatric patient and the reduction in symptom or a change in a disease-relevant laboratory measure comprises an increase in growth. In some embodiments, the increase in growth is measured relative to baseline. In various embodiments, increase in growth is measured as an increase in height Z-score or in weight Z-score. In various embodiments, the increase in height Z-score or in weight Z-score is statistically significant. In various embodiments, the height Z-score, the weight Z-score, or both is increased by at least 0.1, 0.11, 0.12, 0.13, 0.14, 0.15, 0.16, 0.17., 0.18, 0.19, 0.2, 0.21, 0.22, 0.23, 0.24, 0.25, 0.26, 0.27, 0.28, 0.29 0.3, 0.31, 0.32, 0.33, 0.34, 0.35, 0.36, 0.37, 0.38, 0.39 0.4, 0.41, 0.42, 0.43, 0.44, 0.45, 0.46, 0.47, 0.48, 0.49, 0.5, 0.51, 0.52, 0.53, 0.54, 0.55, 0.56, 0.57, 0.58, 0.59, 0.6, 0.7, 0.8, or 0.9 relative to baseline. In some embodiments, the height Z-score, the weight Z-score, or both progressively increases during administration of the ASBTI for a period of about or of at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 48, 50, 60, 70, or 72 weeks.

[00645] In various embodiments, the administration of the ASBTI results in an increase in serum 7αC4 concentration. In various embodiments, the serum 7αC4 concentration is increased by about or at least about 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, or 500 times or fold relative to baseline. In various embodiments the serum 7αC4 concentration is increased about or at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 150%, 200%, 300%, 400%, 500%, 600%, 700%, 800%, 900%, 1,000%, or 10,000% relative to baseline.

[00646] In various embodiments, the administration of the ASBTI results in an increase in the 7αC4:sBA ratio to about or by at least about 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 9,

10, 15, 20, 30, 40, 50, 75, 100, 150, 200, 300, 500, 750, 1,000, 2,000, 3,000, 4,000, 5,000 or 10,000-fold relative to baseline.

[00647] In various embodiments, the administration of the ASBTI results in an increase in fBA excretion. In some embodiments, the administration of the ASBTI results in an increase in fBA excretion of about or of at least about 100%, 110%, 115%, 120%, 130%, 150%, 200%, 250%, 275%, 300%, 400%, 500%, 600%, 700%, 800%, 1,000%, 5,000%, 10,000% or 15,000% relative to baseline. In various embodiments, fBA excretion is increased by about or by at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 fold or times relative to baseline. In some embodiments, fBA excretion is increased by about or by at least about 100 μmol, 150 μmol, 200 μmol, 250 μmol, 300 μmol, 400 μmol, 500 μmol, 600 μmol, 700 μmol, 800 μmol, 900 μmol, 1,000 μmol, or 1,500 μmol relative to baseline. In various embodiments, administration of the ASBTI results in a dose-dependent increase in fBA excretion so that administration of a higher dose of the ASBTI results in a corresponding higher level of fBA excretion. . In various embodiments, the ASBTI is administered at a dose sufficient to result in an increase in bile acid secretion relative to baseline of at least about or of about 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 fold or times relative to baseline.

[00648] In some embodiments, the administration of the ASBTI results in a reduction in severity of pruritus. In various embodiments, the severity of pruritus is measured using an ITCHRO(OBS) score, an ITCHRO score, a CSS score, or a combination thereof. In various embodiments, the administration of the ASBTI results in a reduction in the ITCHRO(OBS) score on a scale of 1 to 4 of about or of at least about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.25, 2.5, or 3 relative to baseline. In various embodiments, the administration of the ASBTI results in a reduction in the ITCHRO score on a scale of 1 to 10 of about or of at least about 0.1, 0.2, 0.3, 0.4, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, or 10. In various embodiments, the administration of the ASBTI results in a reduction of the ITCHRO(OBS) score, the ITCHRO score, or both to zero. In various embodiments, the administration of the ASBTI results in a reduction of the ITCHRO(OBS) score or ITCHRO score to 1.0 or lower. In various embodiments, the administration of the ASBTI results in a reduction of the CSS score by about of at least about 0.1, 0.2, 0.3, 0.4, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.25, 2.5, or 3 relative to baseline. In various embodiments, the administration of the ASBTI results in a reduction of the CSS score to zero. In various embodiments, the administration of the

ASBTI results in a reduction in the CSS score, the ITCHRO(OBS) score, the ITCHRO score, or a combination thereof by about or by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% relative to baseline. In various embodiments, a reduced value relative to baseline of the CSS score, the ITCHRO(OBS) score, the ITCHRO score, or a combination thereof is observed on 10%, 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% of days.

[00649] In various embodiments, administration of the ASBTI results in an increase in a quality of life inventory score or in a quality of life inventory score related to fatigue. The quality of life inventory score can be a health-related quality of life (HRQoL) score. In some embodiments, the HRQoL score is a PedsQL score. In various embodiments, the administration of the ASBTI results an increase in the PedsQL score or in a PedsQL score related to fatigue of about or of at least about 5%, 10%, 15%, 20%, 25%, 30%, 45%, or 50% relative to baseline.

[00650] In various embodiments, the administration of the ASBTI results in the reduction in the symptom or a change in a disease-relevant laboratory measure by about 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12, days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, 24 weeks, 25 weeks, 26 weeks, 27 weeks, 28 weeks, 29 weeks, 30 weeks, 31 weeks, 32 weeks, 33 weeks, 34 weeks, 35 weeks, 36 weeks, 37 weeks, 38 weeks, 39 weeks, 40 weeks, 41 weeks, 42 weeks, 43 weeks, 44 weeks, 45 weeks, 46 weeks, 47 weeks, 48 weeks, 49 weeks, 50 weeks, 51 weeks, 52 weeks, or 1 year.

[00651] In various embodiments, serum bilirubin concentration is at pre-administration baseline levels or at normal levels at about or by about 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 4 months, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, 24 weeks, 25 weeks, 26 weeks, 27 weeks, 28 weeks, 29 weeks, 30 weeks, 31 weeks, 32 weeks, 33 weeks, 34 weeks, 35 weeks, 36 weeks, 37 weeks, 38 weeks, 39 weeks, 40 weeks, 41 weeks, 42 weeks, 43 weeks, 44 weeks, 45 weeks, 46 weeks, 47 weeks, 48 weeks, 49 weeks, 50 weeks, 51 weeks, 52 weeks, or 1 year.

[00652] In various embodiments, serum ALT concentration is at pre-administration baseline levels or at normal levels at about or by about 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 4 months, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, 24 weeks, 25 weeks, 26 weeks, 27 weeks, 28 weeks, 29 weeks, 30 weeks, 31 weeks, 32 weeks, 33 weeks, 34 weeks, 35 weeks, 36 weeks, 37 weeks, 38 weeks, 39 weeks, 40 weeks, 41 weeks, 42 weeks, 43 weeks, 44 weeks, 45 weeks, 46 weeks, 47 weeks, 48 weeks, 49 weeks, 50 weeks, 51 weeks, 52 weeks, or 1 year. In some embodiments, the administration of the ASBTI results in a reduction in ALT levels relative to baseline of about or of at least about 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, or 15%.

[00653] In various embodiments, serum ALT concentration, serum AST concentration, serum bilirubin concentration, or various combinations thereof are within normal range or at pre-administration baseline levels at about or by about 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 4 months, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, 24 weeks, 25 weeks, 26 weeks, 27 weeks, 28 weeks, 29 weeks, 30 weeks, 31 weeks, 32 weeks, 33 weeks, 34 weeks, 35 weeks, 36 weeks, 37 weeks, 38 weeks, 39 weeks, 40 weeks, 41 weeks, 42 weeks, 43 weeks, 44 weeks, 45 weeks, 46 weeks, 47 weeks, 48 weeks, 49 weeks, 50 weeks, 51 weeks, 52 weeks, or 1 year. In various embodiments, the administration of the ASBTI does not result in a statistically significant change from baseline in serum bilirubin concentration, serum AST concentration, serum ALT concentration, serum alkaline phosphatase concentration, or some combination thereof for a period of at least about or of about 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 4 months, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, 24 weeks, 25 weeks, 26 weeks, 27 weeks, 28 weeks, 29 weeks, 30 weeks, 31 weeks, 32 weeks, 33 weeks, 34 weeks, 35 weeks, 36 weeks, 37 weeks, 38 weeks, 39 weeks, 40 weeks, 41 weeks, 42 weeks, 43 weeks, 44 weeks, 45 weeks, 46 weeks, 47 weeks, 48 weeks, 49 weeks, 50 weeks, 51 weeks, 52 weeks, or 1 year.

Pharmaceutical Compositions

[00654] In some embodiments, the ASBTI is administered as a pharmaceutical composition comprising an ASBTI (the composition or the pharmaceutical composition). Any composition described herein can be formulated for ileal, rectal and/or colonic delivery. In more specific embodiments, the composition is formulated for non-systemic or local delivery to the rectum and/or colon. It is to be understood that, as used herein, delivery to the colon includes delivery to sigmoid colon, transverse colon, and/or ascending colon. In still more specific embodiments, the composition is formulated for non-systemic or local delivery to the rectum and/or colon is administered rectally. In other specific embodiments, the composition is formulated for non-systemic or local delivery to the rectum and/or colon is administered orally.

[00655] Provided herein, in certain embodiments, is a pharmaceutical composition comprising a therapeutically effective amount of any compound described herein. In certain instances, the pharmaceutical composition comprises an ASBT inhibitor (e.g., any ASBTI described herein).

[00656] In certain embodiments, pharmaceutical compositions are formulated in a conventional manner using one or more physiologically acceptable carriers including, e.g., excipients and auxiliaries which facilitate processing of the active compounds into preparations which are suitable for pharmaceutical use. In certain embodiments, proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions described herein is found, for example, in Remington: *The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms*, Mareel Decker, New York, N.Y., 1980; and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed. (Lippincott Williams & Wilkins1999), all of which references are incorporated herein in their entirety for all purposes.

[00657] A pharmaceutical composition, as used herein, refers to a mixture of a compound described herein, with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. In certain instances, the pharmaceutical composition facilitates administration of the compound to an individual or cell. In certain embodiments of practicing the methods of treatment or use

provided herein, therapeutically effective amounts of compounds described herein are administered in a pharmaceutical composition to an individual having a disease, disorder, or condition to be treated. In specific embodiments, the individual is a human. As discussed herein, the compounds described herein are either utilized singly or in combination with one or more additional therapeutic agents.

[00658] In certain embodiments, the pharmaceutical formulations described herein are administered to an individual in any manner, including one or more of multiple administration routes, such as, by way of non-limiting example, oral, parenteral (e.g., intravenous, subcutaneous, intramuscular), intranasal, buccal, topical, rectal, or transdermal administration routes.

[00659] In certain embodiments, a pharmaceutical compositions described herein includes one or more compound described herein as an active ingredient in free-acid or free-base form, or in a pharmaceutically acceptable salt form. In some embodiments, the compounds described herein are utilized as an N-oxide or in a crystalline or amorphous form (i.e., a polymorph). In some situations, a compound described herein exists as tautomers. All tautomers are included within the scope of the compounds presented herein. In certain embodiments, a compound described herein exists in an unsolvated or solvated form, wherein solvated forms comprise any pharmaceutically acceptable solvent, e.g., water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be described herein.

[00660] A "carrier" includes, in some embodiments, a pharmaceutically acceptable excipient and is selected on the basis of compatibility with compounds described herein, such as, compounds of any of Formula I-VI, and the release profile properties of the desired dosage form. Exemplary carrier materials include, e.g., binders, suspending agents, disintegration agents, filling agents, surfactants, solubilizers, stabilizers, lubricants, wetting agents, diluents, and the like. See, e.g., *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H. A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms*, Mareel Decker, New York, N.Y., 1980; and *Pharmaceutical Dosage Forms* and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999), all of which references are incorporated herein in their entirety for all purposes.

[00661] Moreover, in certain embodiments, the pharmaceutical compositions described herein are formulated as a dosage form. As such, in some embodiments, provided herein is a dosage form comprising a compound described herein, suitable for administration to an individual. In certain embodiments, suitable dosage forms include, by way of non-limiting example, aqueous oral dispersions, liquids, gels, syrups, elixirs, slurries, suspensions, solid oral dosage forms, aerosols, controlled release formulations, fast melt formulations, effervescent formulations, lyophilized formulations, tablets, powders, pills, dragees, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate release and controlled release formulations.

[00662] In some embodiments, provided herein is a composition comprising an enteroendocrine peptide secretion enhancing agent and, optionally, a pharmaceutically acceptable carrier for alleviating symptoms of cholestasis or a cholestatic liver disease in an individual.

[00663] In certain embodiments, the composition comprises an enteroendocrine peptide secretion enhancing agent and an absorption inhibitor. In specific embodiments, the absorption inhibitor is an inhibitor that inhibits the absorption of the (or at least one of the) specific enteroendocrine peptide secretion enhancing agent with which it is combined. In some embodiments, the composition comprises an enteroendocrine peptide secretion enhancing agent, an absorption inhibitor and a carrier (e.g., an orally suitable carrier or a rectally suitable carrier, depending on the mode of intended administration). In certain embodiments, the composition comprises an enteroendocrine peptide secretion enhancing agent, an absorption inhibitor, a carrier, and one or more of a cholesterol absorption inhibitor, an enteroendocrine peptide, a peptidase inhibitor, a spreading agent, and a wetting agent.

[00664] In other embodiments, the compositions described herein are administered orally for non-systemic delivery of the ASBTI to the rectum and/or colon, including the sigmoid colon, transverse colon, and/or ascending colon. In specific embodiments, compositions formulated for oral administration are, by way of non-limiting example, enterically coated or formulated oral dosage forms, such as, tablets and/or capsules.

Absorption Inhibitors

[00665] In certain embodiments, the composition described herein as being formulated for the non-systemic delivery of ASBTI further includes an absorption inhibitor. As used herein,

an absorption inhibitor includes an agent or group of agents that inhibit absorption of a bile acid/salt.

[00666] Suitable bile acid absorption inhibitors (also described herein as absorption inhibiting agents) may include, by way of non-limiting example, anionic exchange matrices, polyamines, quaternary amine containing polymers, quaternary ammonium salts, polyallylamine polymers and copolymers, colesevelam, colesevelam hydrochloride, CholestaGel (N,N,N-trimethyl-6-(2-propenylamino)-1-hexanaminium chloride polymer with (chloromethyl)oxirane, 2-propen-1-amine and N-2-propenyl-1-decanamine hydrochloride), cyclodextrins, chitosan, chitosan derivatives, carbohydrates which bind bile acids, lipids which bind bile acids, proteins and proteinaceous materials which bind bile acids, and antibodies and albumins which bind bile acids. Suitable cyclodextrins include those that bind bile acids/salts such as, by way of non-limiting example, β-cyclodextrin and hydroxypropyl-β-cyclodextrin. Suitable proteins, include those that bind bile acids/salts such as, by way of non-limiting example, bovine serum albumin, egg albumin, casein, α-acid glycoprotein, gelatin, soy proteins, peanut proteins, almond proteins, and wheat vegetable proteins.

[00667] In certain embodiments the absorption inhibitor is cholestyramine. In specific embodiments, cholestyramine is combined with a bile acid. Cholestyramine, an ion exchange resin, is a styrene polymer containing quaternary ammonium groups crosslinked by divinylbenzene. In other embodiments, the absorption inhibitor is colestipol. In specific embodiments, colestipol is combined with a bile acid. Colestipol, an ion exchange resin, is a copolymer of diethylenetriamine and 1-chloro-2,3-epoxypropane.

[00668] In certain embodiments of the compositions and methods described herein the ASBTI is linked to an absorption inhibitor, while in other embodiments the ASBTI and the absorption inhibitor are separate molecular entities.

Cholesterol Absorption Inhibitors

[00669] In certain embodiments, a composition described herein optionally includes at least one cholesterol absorption inhibitor. Suitable cholesterol absorption inhibitors include, by way of non-limiting example, ezetimibe (SCH 58235), ezetimibe analogs, ACT inhibitors, stigmastanyl phosphorylcholine, stigmastanyl phosphorylcholine analogues, β-lactam cholesterol absorption inhibitors, sulfate polysaccharides, neomycin, plant sponins, plant sterols, phytostanol preparation FM-VP4, Sitostanol, β-sitosterol, acyl-CoA:cholesterol-O-acyltransferase (ACAT) inhibitors, Avasimibe, Implitapide, steroidal glycosides and the like.

Suitable enzetimibe analogs include, by way of non-limiting example, SCH 48461, SCH 58053 and the like. Suitable ACT inhibitors include, by way of non-limiting example, trimethoxy fatty acid anilides such as Cl-976, 3-[decyldimethylsilyl]-N-[2-(4-methylphenyl)-1-phenylethyl]-propanamide, melinamide and the like. β-lactam cholesterol absorption inhibitors include, by way of non-limiting example, βR-4S)-1,4-bis-(4-methoxyphenyl)-3-β-phenylpropyl)-2-azetidinone and the like.

Peptidase Inhibitors

[00670] In some embodiments, the compositions described herein optionally include at least one peptidase inhibitor. Such peptidase inhibitors include, but are not limited to, dipeptidyl peptidase-4 inhibitors (DPP-4), neutral endopeptidase inhibitors, and converting enzyme inhibitors. Suitable dipeptidyl peptidase-4 inhibitors (DPP-4) include, by way of non-limiting example, Vildaglipti, 2.S)-1-{2-[β-hydroxy-1-adamantyl)amino]acetyl}pyrrolidine-2-carbonitrile, Sitagliptin, βR)-3-amino-1-[9-(trifluoromethyl)-1,4,7,8-tetrazabicyclo[4.3.0]nona-6,8-d ien-4-yl]-4-(2,4,5-trifluorophenyl)butan-1-one, Saxagliptin, and (1S,3S,5S)-2-[(2S)-2-amino-2-β-hydroxy-1-adamantyl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile. Such neutral endopeptidase inhibitors include, but are not limited to, Candoxatrilat and Ecadotril.

Spreading Agents/Wetting Agents

[00671] In certain embodiments, the composition described herein optionally comprises a spreading agent. In some embodiments, a spreading agent is utilized to improve spreading of the composition in the colon and/or rectum. Suitable spreading agents include, by way of non-limiting example, hydroxyethylcellulose, hydroxypropymethyl cellulose, polyethylene glycol, colloidal silicon dioxide, propylene glycol, cyclodextrins, microcrystalline cellulose, polyvinylpyrrolidone, polyoxyethylated glycerides, polycarbophil, di-n-octyl ethers, Cetiol™OE, fatty alcohol polyalkylene glycol ethers, Aethoxal™B), 2-ethylhexyl palmitate, Cegesoft™C 24), and isopropyl fatty acid esters.

[00672] In some embodiments, the compositions described herein optionally comprise a wetting agent. In some embodiments, a wetting agent is utilized to improve wettability of the composition in the colon and rectum. Suitable wetting agents include, by way of non-limiting example, surfactants. In some embodiments, surfactants are selected from, by way of non-limiting example, polysorbate (e.g., 20 or 80), stearyl hetanoate, caprylic/capric fatty acid esters of saturated fatty alcohols of chain length C_{12}-C_{18}, isostearyl diglycerol isostearic acid,

sodium dodecyl sulphate, isopropyl myristate, isopropyl palmitate, and isopropyl myristate/isopropyl stearate/isopropyl palmitate mixture.

Vitamins

[00673] In some embodiments, the methods provided herein further comprise administering one or more vitamins.

[00674] In some embodiments, the vitamin is vitamin A, B1, B2, B3, B5, B6, B7, B9, B12, C, D, E, K, folic acid, pantothenic acid, niacin, riboflavin, thiamine, retinol, beta carotene, pyridoxine, ascorbic acid, cholecalciferol, cyanocobalamin, tocopherols, phylloquinone, menaquinone.

[00675] In some embodiments, the vitamin is a fat-soluble vitamin such as vitamin A, D, E, K, retinol, beta carotene, cholecalciferol, tocopherols, phylloquinone. In a preferred embodiment, the fat-soluble vitamin is tocopherol polyethylene glycol succinate (TPGS).

Bile Acid Sequestrants/Binders

[00676] In some embodiments, a labile bile acid sequestrant is an enzyme dependent bile acid sequestrant. In certain embodiments, the enzyme is a bacterial enzyme. In some embodiments, the enzyme is a bacterial enzyme found in high concentration in human colon or rectum relative to the concentration found in the small intestine. Examples of micro-flora activated systems include dosage forms comprising pectin, galactomannan, and/or Azo hydrogels and/or glycoside conjugates (e.g., conjugates of D-galactoside, β-D-xylopyranoside or the like) of the active agent. Examples of gastrointestinal micro-flora enzymes include bacterial glycosidases such as, for example, D-galactosidase, β-D-glucosidase, α-L-arabinofuranosidase, β-D-xylopyranosidase or the like.

[00677] In certain embodiments, a labile bile acid sequestrant is a time-dependent bile acid sequestrant. In some embodiments, a labile bile acid sequestrant releases a bile acid or is degraded after 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 seconds of sequestration. In some embodiments, a labile bile acid sequestrant releases a bile acid or is degraded after 15, 20, 25, 30, 35, 40, 45, 50, or 55 seconds of sequestration. In some embodiments, a labile bile acid sequestrant releases a bile acid or is degraded after 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 minutes of sequestration. In some embodiments, a labile bile acid sequestrant releases a bile acid or is degraded after about 15, 20, 25, 30, 35, 45, 50, or 55 minutes of sequestration. In some embodiments, a labile bile acid sequestrant releases a bile acid or is degraded after about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11,12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 hours of sequestration. In some

embodiments, a labile bile acid sequestrant releases a bile acid or is degraded after 1, 2, or 3 days of sequestration.

[00678] In some embodiments, the labile bile acid sequestrant has a low affinity for bile acid. In certain embodiments, the labile bile acid sequestrant has a high affinity for a primary bile acid and a low affinity for a secondary bile acid.

[00679] In some embodiments, the labile bile acid sequestrant is a pH dependent bile acid sequestrant. In certain embodiments, the pH dependent bile acid sequestrant has a high affinity for bile acid at a pH of 6 or below and a low affinity for bile acid at a pH above 6. In certain embodiments, the pH dependent bile acid sequestrant has a high affinity for bile acid at a pH of 6.5 or below and a low affinity for bile acid at a pH above 6.5. In certain embodiments, the pH dependent bile acid sequestrant has a high affinity for bile acid at a pH of 7 or below and a low affinity for bile acid at a pH above 7. In certain embodiments, the pH dependent bile acid sequestrant has a high affinity for bile acid at a pH of 7.1 or below and a low affinity for bile acid at a pH above 7.1. In certain embodiments, the pH dependent bile acid sequestrant has a high affinity for bile acid at a pH of 7.2 or below and a low affinity for bile acid at a pH above 7.2. In certain embodiments, the pH dependent bile acid sequestrant has a high affinity for bile acid at a pH of 7.3 or below and a low affinity for bile acid at a pH above 7.3. In certain embodiments, the pH dependent bile acid sequestrant has a high affinity for bile acid at a pH of 7.4 or below and a low affinity for bile acid at a pH above 7.4. In certain embodiments, the pH dependent bile acid sequestrant has a high affinity for bile acid at a pH of 7.5 or below and a low affinity for bile acid at a pH above 7.5. In certain embodiments, the pH dependent bile acid sequestrant has a high affinity for bile acid at a pH of 7.6 or below and a low affinity for bile acid at a pH above 7.6. In certain embodiments, the pH dependent bile acid sequestrant has a high affinity for bile acid at a pH of 7.7 or below and a low affinity for bile acid at a pH above 7.7. In certain embodiments, the pH dependent bile acid sequestrant has a high affinity for bile acid at a pH of 7.8 or below and a low affinity for bile acid at a pH above 7.8. In some embodiments, the pH dependent bile acid sequestrant degrades at a pH above 6. In some embodiments, the pH dependent bile acid sequestrant degrades at a pH above 6.5. In some embodiments, the pH dependent bile acid sequestrant degrades at a pH above 7. In some embodiments, the pH dependent bile acid sequestrant degrades at a pH above 7.1. In some embodiments, the pH dependent bile acid sequestrant degrades at a pH above 7.2. In some embodiments, the pH dependent bile acid sequestrant degrades at a pH above 7.3. In some embodiments, the pH dependent bile acid sequestrant

degrades at a pH above 7.4. In some embodiments, the pH dependent bile acid sequestrant degrades at a pH above 7.5. In some embodiments, the pH dependent bile acid sequestrant degrades at a pH above 7.6. In some embodiments, the pH dependent bile acid sequestrant degrades at a pH above 7.7. In some embodiments, the pH dependent bile acid sequestrant degrades at a pH above 7.8. In some embodiments, the pH dependent bile acid sequestrant degrades at a pH above 7.9.

[00680] In certain embodiments, the labile bile acid sequestrant is lignin or a modified lignin. In some embodiments, the labile bile acid sequestrant is a polycationic polymer or copolymer. In certain embodiments, 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; or a combination thereof. In some embodiments, the bile acid binder is cholestyramine, and various compositions including cholestyramine, which are described, for example, in U. S. Pat. Nos. 3,383,281; 3,308,020; 3,769,399; 3,846,541; 3,974,272; 4,172,120; 4,252,790; 4,340,585; 4,814,354; 4,874,744; 4,895,723; 5,695,749; and 6,066, 336, all of which are incorporated herein by reference in their entirety for all purposes. In some embodiments, the bile acid binder is cholestipol or cholesevelam.

Routes of administration, dosage forms, and dosing regimens

[00681] In some embodiments, the compositions described herein, and the compositions administered in the methods described herein are formulated to inhibit bile acid reuptake or reduce serum or hepatic bile acid levels. In certain embodiments, the compositions described herein are formulated for rectal or oral administration. In some embodiments, such formulations are administered rectally or orally, respectively. In some embodiments, the compositions described herein are combined with a device for local delivery of the compositions to the rectum and/or colon (sigmoid colon, transverse colon, or ascending colon). In certain embodiments, for rectal administration the composition described herein are formulated as enemas, rectal gels, rectal foams, rectal aerosols, suppositories, jelly suppositories, or retention enemas. In some embodiments, for oral administration the compositions described herein are formulated for oral administration and enteric delivery to the colon.

[00682] In certain embodiments, the compositions or methods described herein are non-systemic. In some embodiments, compositions described herein deliver the ASBTI to the distal ileum, colon, and/or rectum and not systemically (e.g., a substantial portion of the enteroendocrine peptide secretion enhancing agent is not systemically absorbed). In some embodiments, oral compositions described herein deliver the ASBTI to the distal ileum, colon, and/or rectum and not systemically (e.g., a substantial portion of the enteroendocrine peptide secretion enhancing agent is not systemically absorbed). In some embodiments, rectal compositions described herein deliver the ASBTI to the distal ileum, colon, and/or rectum and not systemically (e.g., a substantial portion of the enteroendocrine peptide secretion enhancing agent is not systemically absorbed). In certain embodiments, non-systemic compositions described herein deliver less than 90% w/w of the ASBTI systemically. In certain embodiments, non-systemic compositions described herein deliver less than 80% w/w of the ASBTI systemically. In certain embodiments, non-systemic compositions described herein deliver less than 70% w/w of the ASBTI systemically. In certain embodiments, non-systemic compositions described herein deliver less than 60% w/w of the ASBT1 systemically. In certain embodiments, non-systemic compositions described herein deliver less than 50% w/w of the ASBTI systemically. In certain embodiments, non-systemic compositions described herein deliver less than 40% w/w of the ASBTI systemically. In certain embodiments, non-systemic compositions described herein deliver less than 30% w/w of the ASBTI systemically. In certain embodiments, non-systemic compositions described herein deliver less than 25% w/w of the ASBTI systemically. In certain embodiments, non-systemic compositions described herein deliver less than 20% w/w of the ASBTI systemically. In certain embodiments, non-systemic compositions described herein deliver less than 15% w/w of the ASBTI systemically. In certain embodiments, non-systemic compositions described herein deliver less than 10% w/w of the ASBTI systemically. In certain embodiments, non-systemic compositions described herein deliver less than 5% w/w of the ASBTI systemically. In some embodiments, systemic absorption is determined in any suitable manner, including the total circulating amount, the amount cleared after administration, or the like.

[00683] In certain embodiments, the compositions and/or formulations described herein are administered at least once a day. In certain embodiments, the formulations containing the ASBTI are administered at least twice a day, while in other embodiments the formulations containing the ASBTI are administered at least three times a day. In certain embodiments, the

formulations containing the ASBTI are administered up to five times a day. It is to be understood that in certain embodiments, the dosage regimen of composition containing the ASBTI described herein to is determined by considering various factors such as the patient's age, sex, and diet.

[00684] The concentration of the ASBTI administered in the formulations described herein ranges from about 1 mM to about 1 M. In certain embodiments the concentration of the ASBTI administered in the formulations described herein ranges from about 1 mM to about 750 mM. In certain embodiments the concentration of the ASBTI administered in the formulations described herein ranges from about 1 mM to about 500 mM. In certain embodiments the concentration of the ASBTI administered in the formulations described herein ranges from about 5 mM to about 500 mM. In certain embodiments the concentration of the ASBTI administered in the formulations described herein ranges from about 10 mM to about 500 mM. In certain embodiments the concentration of the administered in the formulations described herein ranges from about 25 mM to about 500 mM. In certain embodiments the concentration of the ASBTI administered in the formulations described herein ranges from about 50 mM to about 500 mM. In certain embodiments the concentration of the ASBTI administered in the formulations described herein ranges from about 100 mM to about 500 mM. In certain embodiments the concentration of the ASBTI administered in the formulations described herein ranges from about 200 mM to about 500 mM.

[00685] In certain embodiments, by targeting the distal gastrointestinal tract (e.g., distal ileum, colon, and/or rectum), compositions and methods described herein provide efficacy (e.g., in reducing microbial growth and/or alleviating symptoms of cholestasis or a cholestatic liver disease) with a reduced dose of enteroendocrine peptide secretion enhancing agent (e.g., as compared to an oral dose that does not target the distal gastrointestinal tract).

Rectal Administration Formulations

[00686] The pharmaceutical compositions described herein for the non-systemic delivery of a compound described herein to the rectum and/or colon are formulated for rectal administration as rectal enemas, rectal foams, rectal gels, and rectal suppositories. The components of such formulations are described herein. It is to be understood that as used herein, pharmaceutical compositions and compositions are or comprise the formulations as described herein. In some embodiments, rectal formulations comprise rectal enemas, foams, gels, or suppositories.

[00687] In certain embodiments, liquid carrier vehicles or co-solvents in the compositions and/or formulations described herein include, by way of non-limiting example, purified water, propylene glycol, PEG200, PEG300, PEG400, PEG600, polyethyleneglycol, ethanol, 1-propanol, 2-propanol, 1-propen-3-ol (allyl alcohol), propylene glycol, glycerol, 2-methyl-2-propanol, formamide, methyl formamide, dimethyl formamide, ethyl formamide, diethyl formamide, acetamide, methyl acetamide, dimethyl acetamide, ethyl acetamide, diethyl acetamide, 2-pyrrolidone, N-methyl-2-pyrrolidone, N-ethyl-2-pyrrolidone, tetramethyl urea, 1,3-dimethyl-2-imidazolidinone, propylene carbonate, 1,2-butylene carbonate, 2,3-butylene carbonate, dimethyl sulfoxide, diethyl sulfoxide, hexamethyl phosphoramide, pyruvic aldehyde dimethylacetal, dimethylisosorbide and combinations thereof.

[00688] In some embodiments, stabilizers used in compositions and/or formulations described herein include, but are not limited to, partial glycerides of polyoxyethylenic saturated fatty acids.

[00689] In certain embodiments, surfactants/emulsifiers used in the compositions and/or formulations described herein include, by way of non-limiting example, mixtures of cetostearylic alcohol with sorbitan esterified with polyoxyethylenic fatty acids, polyoxyethylene fatty ethers, polyoxyethylene fatty esters, fatty acids, sulfated fatty acids, phosphated fatty acids, sulfosuccinates, amphoteric surfactants, non-ionic poloxamers, non-ionic meroxapols, petroleum derivatives, aliphatic amines, polysiloxane derivatives, sorbitan fatty acid esters, laureth-4, PEG-2 dilaurate, stearic acid, sodium lauryl sulfate, dioctyl sodium sulfosuccinate, cocoamphopropionate, poloxamer 188, meroxapol 258, triethanolamine, dimethicone, polysorbate 60, sorbitan monostearate, pharmaceutically acceptable salts thereof, and combinations thereof.

[00690] In some embodiments, non-ionic surfactants used in compositions and/or formulations described herein include, by way of non-limiting example, phospholipids, alkyl poly(ethylene oxide), poloxamers (e.g., poloxamer 188), polysorbates, sodium dioctyl sulfosuccinate, Brij™-30 (Laureth-4), Brij™-58 (Ceteth-20) and Brij™-78 (Steareth-20), Brij™-721 (Steareth-21), Crillet-1 (Polysorbate 20), Crillet-2 (Polysorbate 40), Crillet-3 (Polysorbate 60), Crillet 45 (Polysorbate 80), Myrj-52 (PEG-40 Stearate), Myrj-53 (PEG-50 Stearate), Pluronic™ F77 (Poloxamer 217), Pluronic™ F87 (Poloxamer 237), Pluronic™ F98 (Poloxamer 288), Pluronic™ L62 (Poloxamer 182), Pluronic™ L64 (Poloxamer 184), Pluronic™ F68 (Poloxamer 188), Pluronic™ L81 (Poloxamer 231), Pluronic™ L92 (Poloxamer 282), Pluronic™ L101 (Poloxamer 331), Pluronic™ P103 (Poloxamer 333),

Pluracare™ F 108 NF (Poloxamer 338), and Pluracare™ F 127 NF (Poloxamer 407) and combinations thereof. Pluronic™ polymers are commercially purchasable from BASF, USA and Germany.

[00691] In certain embodiments, anionic surfactants used in compositions and/or formulations described herein include, by way of non-limiting example, sodium laurylsulphate, sodium dodecyl sulfate (SDS), ammonium lauryl sulfate, alkyl sulfate salts, alkyl benzene sulfonate, and combinations thereof.

[00692] In some embodiments, the cationic surfactants used in compositions and/or formulations described herein include, by way of non-limiting example, benzalkonium chloride, benzethonium chloride, cetyl trimethylammonium bromide, hexadecyl trimethyl ammonium bromide, other alkyltrimethylammonium salts, cetylpyridinium chloride, polyethoxylated tallow and combinations thereof.

[00693] In certain embodiments, the thickeners used in compositions and/or formulations described herein include, by way of non-limiting example, natural polysaccharides, semi-synthetic polymers, synthetic polymers, and combinations thereof. Natural polysaccharides include, by way of non-limiting example, acacia, agar, alginates, carrageenan, guar, arabic, tragacanth gum, pectins, dextran, gellan and xanthan gums. Semi-synthetic polymers include, by way of non-limiting example, cellulose esters, modified starehes, modified celluloses, carboxymethylcellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Synthetic polymers include, by way of non-limiting example, polyoxyalkylenes, polyvinyl alcohol, polyacrylamide, polyacrylates, carboxypolymethylene (carbomer), polyvinylpyrrolidone (povidones), polyvinylacetate, polyethylene glycols and poloxamer. Other thickeners include, by way of nonlimiting example, polyoxyethyleneglycol isostearate, cetyl alcohol, Polyglycol 300 isostearate, propyleneglycol, collagen, gelatin, and fatty acids (e.g., lauric acid, myristic acid, palmitic acid, stearic acid, palmitoleic acid, linoleic acid, linolenic acid, oleic acid and the like).

[00694] In some embodiments, chelating agents used in the compositions and/or formulations described herein include, by way of non-limiting example, ethylenediaminetetraacetic acid (EDTA) or salts thereof, phosphates and combinations thereof.

[00695] In some embodiments, the concentration of the chelating agent or agents used in the rectal formulations described herein is a suitable concentration, e.g., about 0.1%, 0.15%, 0.2%, 0.25%, 0.3%, 0.4%, or 0.5% (w/v).

[00696] In some embodiments, preservatives used in compositions and/or formulations described herein include, by way of non-limiting example, parabens, ascorbyl palmitate, benzoic acid, butylated hydroxyanisole, butylated hydroxytoluene, chlorobutanol, ethylenediamine, ethylparaben, methylparaben, butyl paraben, propylparaben, monothioglycerol, phenol, phenylethyl alcohol, propylparaben, sodium benzoate, sodium propionate, sodium formaldehyde sulfoxylate, sodium metabisulfite, sorbic acid, sulfur dioxide, maleic acid, propyl gallate, benzalkonium chloride, benzethonium chloride, benzyl alcohol, chlorhexidine acetate, chlorhexidine gluconate, sorbic acid, potassium sorbitol, chlorbutanol, phenoxyethanol, cetylpyridinium chloride, phenylmercuric nitrate, thimerosol, and combnations thereof.

[00697] In certain embodiments, antioxidants used in compositions and/or formulations described herein include, by way of non-limiting example, ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorous acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium sulfite, sodium bisulfite, sodium formaldehyde sulfoxylate, potassium metabisulphite, sodium metabisulfite, oxygen, quinones, t-butyl hydroquinone, erythorbic acid, olive (olea eurpaea) oil, pentasodium penetetate, pentetic acid, tocopheryl, tocopheryl acetate and combinations thereof.

[00698] In some embodiments, concentration of the antioxidant or antioxidants used in the rectal formulations described herein is sufficient to achieve a desired result, e.g., about 0.1%, 0.15%, 0.2%, 0.25%, 0.3%, 0.4%, or 0.5% (w/v).

[00699] The lubricating agents used in compositions and/or formulations described herein include, by way of non-limiting example, natural or synthetic fat or oil (e.g., a tris-fatty acid glycerate and the like). In some embodiments, lubricating agents include, by way of non-limiting example, glycerin (also called glycerine, glycerol, 1,2,3-propanetriol, and trihydroxypropane), polyethylene glycols (PEGs), polypropylene glycol, polyisobutene, polyethylene oxide, behenic acid, behenyl alcohol, sorbitol, mannitol, lactose, polydimethylsiloxane and combinations thereof.

[00700] In certain embodiments, mucoadhesive and/or bioadhesive polymers are used in the compositions and/or formulations described herein as agents for inhibiting absorption of the enteroendocrine peptide secretion enhancing agent across the rectal or colonic mucosa.

Bioadhesive or mucoadhesive polymers include, by way of non-limiting example, hydroxypropyl cellulose, polyethylene oxide homopolymers, polyvinyl ether-maleic acid copolymers, methyl cellulose, ethyl cellulose, propyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmcthyl cellulose, carboxymethylcellulose, polycarbophil, polyvinylpyrrolidone, carbopol, polyurethanes, polyethylene oxide-polypropyline oxide copolymers, sodium carboxymethyl cellulose, polyethylene, polypropylene, lectins, xanthan gum, alginates, sodium alginate, polyacrylic acid, chitosan, hyaluronic acid and ester derivatives thereof, vinyl acetate homopolymer, calcium polycarbophil, gelatin, natural gums, karaya, tragacanth, algin, chitosan, starehes, pectins, and combinations thereof.

[00701] In some embodiments, buffers/pH adjusting agents used in compositions and/or formulations described herein include, by way of non-limiting example, phosphoric acid, monobasic sodium or potassium phosphate, triethanolamine (TRIS), BICINE, HEPES, Trizma, glycine, histidine, arginine, lysine, asparagine, aspartic acid, glutamine, glutamic acid, carbonate, bicarbonate, potassium metaphosphate, potassium phosphate, monobasic sodium acetate, acetic acid, acetate, citric acid, sodium citrate anhydrous, sodium citrate dihydrate and combinations thereof. In certain embodiments, an acid or a base is added to adjust the pH. Suitable acids or bases include, by way of non-limiting example, HCL, NaOH and KOH.

[00702] In certain embodiments, concentration of the buffering agent or agents used in the rectal formulations described herein is sufficient to achieve or maintain a physiologically desirable pH, e.g., about 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.8%, 0.9%, or 1.0% (w/w).

[00703] The tonicity modifiers used in compositions and/or formulations described herein include, by way of non-limiting example, sodium chloride, potassium chloride, sodium phosphate, mannitol, sorbitol or glucose.

Oral Administration for Colonic Delivery

[00704] In certain aspects, the composition or formulation containing one or more compounds described herein is orally administered for local delivery of an ASBTI, or a compound described herein to the colon and/or rectum. Unit dosage forms of such compositions include a pill, tablet or capsules formulated for enteric delivery to colon. In certain embodiments, such pills, tablets or capsule contain the compositions described herein entrapped or embedded in microspheres. In some embodiments, microspheres include, by

way of non-limiting example, chitosan microcores HPMC capsules and cellulose acetate butyrate (CAB) microspheres. In certain embodiments, oral dosage forms are prepared using conventional methods known to those in the field of pharmaceutical formulation. For example, in certain embodiments, tablets are manufactured using standard tablet processing procedures and equipment. An exemplary method for forming tablets is by direct compression of a powdered, crystalline or granular composition containing the active agent(s), alone or in combination with one or more carriers, additives, or the like. In alternative embodiments, tablets are prepared using wet-granulation or dry-granulation processes. In some embodiments, tablets are molded rather than compressed, starting with a moist or otherwise tractable material.

[00705] In certain embodiments, tablets prepared for oral administration contain various excipients, including, by way of non-limiting example, binders, diluents, lubricants, disintegrants, fillers, stabilizers, surfactants, preservatives, coloring agents, flavoring agents and the like. In some embodiments, binders are used to impart cohesive qualities to a tablet, ensuring that the tablet remains intact after compression. Suitable binder materials include, by way of non-limiting example, stareh (including corn stareh and pregelatinized stareh), gelatin, sugars (including sucrose, glucose, dextrose and lactose), polyethylene glycol, propylene glycol, waxes, and natural and synthetic gums, e.g., acacia sodium alginate, polyvinylpyrrolidone, cellulosic polymers (including hydroxypropyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, and the like), Veegum, and combinations thereof. In certain embodiments, diluents are utilized to increase the bulk of the tablet so that a practical size tablet is provided. Suitable diluents include, by way of non-limiting example, dicalcium phosphate, calcium sulfate, lactose, cellulose, kaolin, mannitol, sodium chloride, dry stareh, powdered sugar and combinations thereof. In certain embodiments, lubricants are used to facilitate tablet manufacture; examples of suitable lubricants include, by way of non-limiting example, vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil, and oil of theobroma, glycerin, magnesium stearate, calcium stearate, stearic acid and combinations thereof. In some embodiments, disintegrants are used to facilitate disintegration of the tablet, and include, by way of non-limiting example, starehes, clays, celluloses, algins, gums, crosslinked polymers and combinations thereof. Fillers include, by way of non-limiting example, materials such as silicon dioxide, titanium dioxide, alumina, talc, kaolin, powdered cellulose and microcrystalline cellulose, as well as soluble materials such as mannitol, urea, sucrose,

lactose, dextrose, sodium chloride and sorbitol. In certain embodiments, stabilizers are used to inhibit or retard drug decomposition reactions that include, by way of example, oxidative reactions. In certain embodiments, surfactants are anionic, cationic, amphoteric or nonionic surface active agents.

[00706] In some embodiments, ASBTIs, or other compounds described herein are orally administered in association with a carrier suitable for delivery to the distal gastrointestinal tract (e.g., distal ileum, colon, and/or rectum).

[00707] In certain embodiments, a composition described herein comprises an ASBTI, or other compounds described herein in association with a matrix (e.g., a matrix comprising hypermellose) that allows for controlled release of an active agent in the distal part of the ileum and/or the colon. In some embodiments, a composition comprises a polymer that is pH sensitive (e.g., a MMX™ matrix from Cosmo Pharmaceuticals) and allows for controlled release of an active agent in the distal part of the ileum. Examples of such pH sensitive polymers suitable for controlled release include and are not limited to polyacrylic polymers (e.g., anionic polymers of methacrylic acid and/or methacrylic acid esters, e.g., Carbopol® polymers) that comprise acidic groups (e.g., —COOH, —SO_3H) and swell in basic pH of the intestine (e.g., pH of about 7 to about 8). In some embodiments, a composition suitable for controlled release in the distal ileum comprises microparticulate active agent (e.g., micronized active agent). In some embodiments, a non-enzymatically degrading poly(dl-lactide-co-glycolide) (PLGA) core is suitable for delivery of an enteroendocrine peptide secretion enhancing agent to the distal ileum. In some embodiments, a dosage form comprising an enteroendocrine peptide secretion enhancing agent is coated with an enteric polymer (e.g., Eudragit® S-100, cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethylcellulose phthalate, anionic polymers of methacrylic acid, methacrylic acid esters or the like) for site specific delivery to the distal ileum and/or the colon. In some embodiments, bacterially activated systems are suitable for targeted delivery to the distal part of the ileum. Examples of micro-flora activated systems include dosage forms comprising pectin, galactomannan, and/or Azo hydrogels and/or glycoside conjugates (e.g., conjugates of D-galactoside, β-D-xylopyranoside or the like) of the active agent. Examples of gastrointestinal micro-flora enzymes include bacterial glycosidases such as, for example, D-galactosidase, β-D-glucosidase, α-L-arabinofuranosidase, β-D-xylopyranosidase or the like.

[00708] The pharmaceutical composition described herein optionally include an additional therapeutic compound described herein and one or more pharmaceutically acceptable

additives such as a compatible carrier, binder, filling agent, suspending agent, flavoring agent, sweetening agent, disintegrating agent, dispersing agent, surfactant, lubricant, colorant, diluent, solubilizer, moistening agent, plasticizer, stabilizer, penetration enhancer, wetting agent, anti-foaming agent, antioxidant, preservative, or one or more combination thereof. In some aspects, using standard coating procedures, such as those described in Remington's Pharmaceutical Sciences, 20th Edition (2000), a film coating is provided around the formulation of the compound of Formula I. In one embodiment, a compound described herein is in the form of a particle and some or all of the particles of the compound are coated. In certain embodiments, some or all of the particles of a compound described herein are microencapsulated. In some embodiments, the particles of the compound described herein are not microencapsulated and are uncoated.

[00709] In further embodiments, a tablet or capsule comprising an ASBTI or other compounds described herein is film-coated for delivery to targeted sites within the gastrointestinal tract. Examples of enteric film coats include and are not limited to hydroxypropylmethylcellulose, polyvinyl pyrrolidone, hydroxypropyl cellulose, polyethylene glycol 3350, 4500, 8000, methyl cellulose, pseudoethylcellulose, amylopectin and the like.

Pediatric Dosage Formulations and Compositions

[00710] Provided herein, in certain embodiments, is a pediatric dosage formulation or composition comprising a therapeutically effective amount of any compound described herein. In certain instances, the pharmaceutical composition comprises an ASBT inhibitor (e.g., any ASBTI described herein).

[00711] In certain embodiments, suitable dosage forms for the pediatric dosage formulation or composition include, by way of non-limiting example, aqueous or non-aqueous oral dispersions, liquids, gels, syrups, elixirs, slurries, suspensions, solutions, controlled release formulations, fast melt formulations, effervescent formulations, lyophilized formulations, chewable tablets, gummy candy, orally disintegrating tablets, powders for reconstitution as suspension or solution, sprinkle oral powder or granules, dragees, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate release and controlled release formulations. In some embodiments, provided herein is a pharmaceutical composition wherein the pediatric 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, orally disintegrating strip, sachet, and sprinkle oral powder or granules.

[00712] In another aspect, provide herein is a pharmaceutical composition wherein at least one excipient is a flavoring agent or a sweetener. In some embodiments, provided herein is a coating. In some embodiments, provided herein is a taste-masking technology selected from coating of drug particles with a taste-neutral polymer by spray-drying, wet granulation, fluidized bed, and microencapsulation; coating with molten waxes of a mixture of molten waxes and other pharmaceutical adjuvants; entrapment of drug particles by complexation, flocculation or coagulation of an aqueous polymeric dispersion; adsorption of drug particles on resin and inorganic supports; and solid dispersion wherein a drug and one or more taste neutral compounds are melted and cooled, or co-precipitated by a solvent evaporation. In some embodiments, provided herein is a delayed or sustained release formulation comprising drug particles or granules in a rate controlling polymer or matrix.

[00713] Suitable sweeteners include sucrose, glucose, fructose or intense sweeteners, i.e. agents with a high sweetening power when compared to sucrose (e.g. at least 10 times sweeter than sucrose). Suitable intense sweeteners comprise aspartame, saccharin, sodium or potassium or calcium saccharin, acesulfame potassium, sucralose, alitame, xylitol, cyclamate, neomate, neohesperidine dihydrochalcone or mixtures thereof, thaumatin, palatinit, stevioside, rebaudioside, Magnasweet®. The total concentration of the sweeteners may range from effectively zero to about 300 mg/ml based on the liquid composition upon reconstitution.

[00714] In order to increase the palatability of the liquid composition upon reconstitution with an aqueous medium, one or more taste-making agents may be added to the composition in order to mask the taste of the ASBT inhibitor. A taste-masking agent can be a sweetener, a flavoring agent or a combination thereof. The taste-masking agents typically provide up to about 0.1% or 5% by weight of the total pharmaceutical composition. In a preferred embodiment of the present invention, the composition contains both sweetener(s) and flavor(s).

[00715] A flavoring agent herein is a substance capable of enhancing taste or aroma of a composition. Suitable natural or synthetic flavoring agents can be selected from standard reference books, for example Fenaroli's Handbook of Flavor Ingredients, 3rd edition (1995). Non-limiting examples of flavoring agents and/or sweeteners useful in the formulations described herein, include, e.g., acacia syrup, acesulfame K, alitame, anise, apple, aspartame,

banana, Bavarian cream, berry, black currant, butterscotch, calcium citrate, camphor, caramel, cherry, cherry cream, chocolate, cinnamon, bubble gum, citrus, citrus punch, citrus cream, cotton candy, cocoa, cola, cool cherry, cool citrus, cyclamate, cylamate, dextrose, *eucalyptus*, eugenol, fructose, fruit punch, ginger, glycyrrhetinate, *glycyrrhiza* (licorice) syrup, grape, grapefruit, honey, isomalt, lemon, lime, lemon cream, monoammonium glyrrhizinate (MagnaSweet®), maltol, mannitol, maple, marshmallow, menthol, mint cream, mixed berry, neohesperidine DC, neotame, orange, pear, peach, peppermint, peppermint cream, Prosweet® Powder, raspberry, root beer, rum, saccharin, safrole, sorbitol, spearmint, spearmint cream, strawberry, strawberry cream, *stevia*, sucralose, sucrose, sodium saccharin, saccharin, aspartame, acesulfame potassium, mannitol, talin, sylitol, sucralose, sorbitol, Swiss cream, tagatose, tangerine, thaumatin, tutti fruitti, vanilla, walnut, watermelon, wild cherry, wintergreen, xylitol, or any combination of these flavoring ingredients, e.g., anise-menthol, cherry-anise, cinnamon-orange, cherry-cinnamon, chocolate-mint, honey-lemon, lemon-lime, lemon-mint, menthol-*eucalyptus*, orange-cream, vanilla-mint, and mixtures thereof. Flavoring agents can be used singly or in combinations of two or more. In some embodiments, the aqueous liquid dispersion comprises a sweetening agent or flavoring agent in a concentration ranging from about 0.001% to about 5.0% the volume of the aqueous dispersion. In one embodiment, the aqueous liquid dispersion comprises a sweetening agent or flavoring agent in a concentration ranging from about 0.001% to about 1.0% the volume of the aqueous dispersion. In another embodiment, the aqueous liquid dispersion comprises a sweetening agent or flavoring agent in a concentration ranging from about 0.005% to about 0.5% the volume of the aqueous dispersion. In yet another embodiment, the aqueous liquid dispersion comprises a sweetening agent or flavoring agent in a concentration ranging from about 0.01% to about 1.0% the volume of the aqueous dispersion. In yet another embodiment, the aqueous liquid dispersion comprises a sweetening agent or flavoring agent in a concentration ranging from about 0.01% to about 0.5% the volume of the aqueous dispersion.

[00716] In certain embodiments, a pediatric pharmaceutical composition described herein includes one or more compound described herein as an active ingredient in free-acid or free-base form, or in a pharmaceutically acceptable salt form. In some embodiments, the compounds described herein are utilized as an N-oxide or in a crystalline or amorphous form (i.e., a polymorph). In some situations, a compound described herein exists as tautomers. All tautomers are included within the scope of the compounds presented herein. In certain

embodiments, a compound described herein exists in an unsolvated or solvated form, wherein solvated forms comprise any pharmaceutically acceptable solvent, e.g., water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be described herein.

[00717] A "carrier" for pediatric pharmaceutical compositions includes, in some embodiments, a pharmaceutically acceptable excipient and is selected on the basis of compatibility with compounds described herein, such as, compounds of any of Formula I-VI, and the release profile properties of the desired dosage form. Exemplary carrier materials include, e.g., binders, suspending agents, disintegration agents, filling agents, surfactants, solubilizers, stabilizers, lubricants, wetting agents, diluents, and the like. See, e.g., *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pa. 1975; Liberman, H. A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms*, Marcel Decker, New York, N.Y., 1980; and *Pharmaceutical Dosage* Forms *and* Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins 1999), all of which references are incorporated herein by reference in their entirety for all purposes.

[00718] Moreover, in certain embodiments, the pediatric pharmaceutical compositions described herein are formulated as a dosage form. As such, in some embodiments, provided herein is a dosage form comprising a compound described herein, suitable for administration to an individual. In certain embodiments, suitable dosage forms include, by way of non-limiting example, aqueous oral dispersions, liquids, gels, syrups, elixirs, slurries, suspensions, solid oral dosage forms, aerosols, controlled release formulations, fast melt formulations, effervescent formulations, lyophilized formulations, tablets, powders, pills, dragees, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate release and controlled release formulations.

[00719] In certain aspects, the pediatric composition or formulation containing one or more compounds described herein is orally administered for local delivery of an ASBTI, or a compound described herein to the colon and/or rectum. Unit dosage forms of such compositions include a pill, tablet or capsules formulated for enteric delivery to colon. In certain embodiments, such pills, tablets or capsule contain the compositions described herein entrapped or embedded in microspheres. In some embodiments, microspheres include, by

way of non-limiting example, chitosan microcores HPMC capsules and cellulose acetate butyrate (CAB) microspheres. In certain embodiments, oral dosage forms are prepared using conventional methods known to those in the field of pharmaceutical formulation. For example, in certain embodiments, tablets are manufactured using standard tablet processing procedures and equipment. An exemplary method for forming tablets is by direct compression of a powdered, crystalline or granular composition containing the active agent(s), alone or in combination with one or more carriers, additives, or the like. In alternative embodiments, tablets are prepared using wet-granulation or dry-granulation processes. In some embodiments, tablets are molded rather than compressed, starting with a moist or otherwise tractable material.

[00720] In certain embodiments, tablets prepared for oral administration contain various excipients, including, by way of non-limiting example, binders, diluents, lubricants, disintegrants, fillers, stabilizers, surfactants, preservatives, coloring agents, flavoring agents and the like. In some embodiments, binders are used to impart cohesive qualities to a tablet, ensuring that the tablet remains intact after compression. Suitable binder materials include, by way of non-limiting example, starch (including corn starch and pregelatinized starch), gelatin, sugars (including sucrose, glucose, dextrose and lactose), polyethylene glycol, propylene glycol, waxes, and natural and synthetic gums, e.g., acacia sodium alginate, polyvinylpyrrolidone, cellulosic polymers (including hydroxypropyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, and the like), Veegum, and combinations thereof. In certain embodiments, diluents are utilized to increase the bulk of the tablet so that a practical size tablet is provided. Suitable diluents include, by way of non-limiting example, dicalcium phosphate, calcium sulfate, lactose, cellulose, kaolin, mannitol, sodium chloride, dry starch, powdered sugar and combinations thereof. In certain embodiments, lubricants are used to facilitate tablet manufacture; examples of suitable lubricants include, by way of non-limiting example, vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil, and oil of *theobroma*, glycerin, magnesium stearate, calcium stearate, stearic acid and combinations thereof. In some embodiments, disintegrants are used to facilitate disintegration of the tablet, and include, by way of non-limiting example, starches, clays, celluloses, algins, gums, crosslinked polymers and combinations thereof. Fillers include, by way of non-limiting example, materials such as silicon dioxide, titanium dioxide, alumina, talc, kaolin, powdered cellulose and microcrystalline cellulose, as well as soluble materials such as mannitol, urea, sucrose,

lactose, dextrose, sodium chloride and sorbitol. In certain embodiments, stabilizers are used to inhibit or retard drug decomposition reactions that include, by way of example, oxidative reactions. In certain embodiments, surfactants are anionic, cationic, amphoteric or nonionic surface active agents.

[00721] In some embodiments, ASBTIs, or other compounds described herein are orally administered in association with a carrier suitable for delivery to the distal gastrointestinal tract (e.g., distal ileum, colon, and/or rectum).

[00722] In certain embodiments, a pediatric composition described herein comprises an ASBTI, or other compounds described herein in association with a matrix (e.g., a matrix comprising hypermellose) that allows for controlled release of an active agent in the distal part of the ileum and/or the colon. In some embodiments, a composition comprises a polymer that is pH sensitive (e.g., a MMX™ matrix from Cosmo Pharmaceuticals) and allows for controlled release of an active agent in the distal part of the ileum. Examples of such pH sensitive polymers suitable for controlled release include and are not limited to polyacrylic polymers (e.g., anionic polymers of methacrylic acid and/or methacrylic acid esters, e.g., Carbopol® polymers) that comprise acidic groups (e.g., —COOH, —SO_3H) and swell in basic pH of the intestine (e.g., pH of about 7 to about 8). In some embodiments, a composition suitable for controlled release in the distal ileum comprises microparticulate active agent (e.g., micronized active agent). In some embodiments, a non-enzymatically degrading poly(dl-lactide-co-glycolide) (PLGA) core is suitable for delivery of an enteroendocrine peptide secretion enhancing agent to the distal ileum. In some embodiments, a dosage form comprising an enteroendocrine peptide secretion enhancing agent is coated with an enteric polymer (e.g., Eudragit® S-100, cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethylcellulose phthalate, anionic polymers of methacrylic acid, methacrylic acid esters or the like) for site specific delivery to the distal ileum and/or the colon. In some embodiments, bacterially activated systems are suitable for targeted delivery to the distal part of the ileum. Examples of micro-flora activated systems include dosage forms comprising pectin, galactomannan, and/or Azo hydrogels and/or glycoside conjugates (e.g., conjugates of D-galactoside, β-D-xylopyranoside or the like) of the active agent. Examples of gastrointestinal micro-flora enzymes include bacterial glycosidases such as, for example, D-galactosidase, β-D-glucosidase, α-L-arabinofuranosidase, β-D-xylopyranosidase or the like.

[00723] The pediatric pharmaceutical composition described herein optionally include an additional therapeutic compound described herein and one or more pharmaceutically acceptable additives such as a compatible carrier, binder, filling agent, suspending agent, flavoring agent, sweetening agent, disintegrating agent, dispersing agent, surfactant, lubricant, colorant, diluent, solubilizer, moistening agent, plasticizer, stabilizer, penetration enhancer, wetting agent, anti-foaming agent, antioxidant, preservative, or one or more combination thereof. In some aspects, using standard coating procedures, such as those described in *Remington's Pharmaceutical Sciences,* 20th Edition (2000), a film coating is provided around the formulation of the compound of Formula I. In one embodiment, a compound described herein is in the form of a particle and some or all of the particles of the compound are coated. In certain embodiments, some or all of the particles of a compound described herein are microencapsulated. In some embodiments, the particles of the compound described herein are not microencapsulated and are uncoated.

[00724] In further embodiments, a tablet or capsule comprising an ASBTI or other compounds described herein is film-coated for delivery to targeted sites within the gastrointestinal tract. Examples of enteric film coats include and are not limited to hydroxypropylmethylcellulose, polyvinyl pyrrolidone, hydroxypropyl cellulose, polyethylene glycol 3350, 4500, 8000, methyl cellulose, pseudo ethylcellulose, amylopectin and the like.

Solid Dosage Forms for Pediatric Administration

[00725] Solid dosage forms for pediatric administration of the present invention can be manufactured by standard manufacturing techniques. Non-limiting examples of oral solid dosage forms for pediatric administration are described below.

Effervescent Compositions

[00726] The effervescent compositions of the invention may be prepared according to techniques well-known in the art of pharmacy.

[00727] Effervescent formulations contain and effervescent couple of a base component and an acid component, which components reach in the presence of water to generate a gas. In some embodiments, the base component may comprise, for example, an alkali metal or alkaline earth metal carbonate, or bicarbonate. The acid component may comprise, for example, an aliphatic carboxylic acid or a salt thereof, such as citric acid. The base and acid components may each independently constitute, for example, 25% to 55% (w/w) of the

effervescent composition. The ratio of acid component to base component may be within the range of 1:2 to 2:1.

[00728] The effervescent compositions of the invention may be formulated using additional pharmaceutically acceptable carriers or excipients as appropriate. For example, one or more taste masking agents may be used. Dyes may also be used, as pediatric patients often prefer colorful pharmaceutical combinations. The compositions may take the form of, for example, tablets, granules or powders, granules or powders presented in a sachet.

Chewable Tablets

[00729] The chewable tablets of the invention may be prepared according to techniques well-known in the art of pharmacy.

[00730] Chewable tablets are tablets that are intended to disintegrate in the mouth under the action of chewing or sucking and where, in consequence, the active ingredient has greater opportunity to come into contact with the bitter-taste receptors on the tongue.

[00731] One method of overcoming this issue is to absorb the active ingredient onto a suitable substrate. This approach is known in the art and described for example in U.S. Pat. No. 4,647,459, which is incorporated herein by reference in its entirety for all purposes.

[00732] Another approach involves forming the active ingredient into an aggregate along with a pre-swelled substantially anhydrous hydrocolloid. The hydrocolloid absorbs saliva and acquires a slippery texture which enables it to lubricate the particles of aggregate and mask the taste of the active ingredient. This approach is known in the art and described for example in European patent application 0190826, which is incorporated herein by reference in its entirety for all purposes.

[00733] Another approach involves employing a water-insoluble hygroscopic excipient such as microcrystalline cellulose. This approach is known in the art and described for example in U.S. Pat. No. 5,275,823, which is incorporated herein by reference in its entirety for all purposes.

[00734] In addition to the above approaches, the chewable tablets of the present invention can also contain other standard tableting excipients such as a disintegrant and a taste-masking agent.

Orodispersible Tablets

[00735] The orodispersible tablets of the invention may be prepared according to techniques well-known in the art of pharmacy.

[00736] In orodispersible tablets of the invention, the excipient mixtures are such as to provide it with a disintegration rate so that its disintegration in the buccal cavity occurs in an extremely short time and especially shorter than sixty seconds. In some embodiments, the excipient mixture is characterized by the fact that the active substance is in the form of coated or non-coated microcrystals of microgranules. In some embodiments, the orodispersible tablet comprises one or several disintegrating agents of the carboxymethylcellulose type or insoluble reticulated PVP type, one or several swelling agents which may comprise a carboxymethylcellulose, a starch, a modified starch, or a microcrystalline cellulose or optionally a direct compression sugar.

Powders for Reconstitution

[00737] The powder for reconstitution pharmaceutical compositions of the invention may be prepared according to techniques well-known in the art of pharmacy.

[00738] In some embodiments, the powder for reconstitution compositions of the invention comprise an effective amount of at least one internal dehydrating agent. The internal dehydrating agent can enhance the stability of the powder. In some embodiments, the internal dehydrating agent is magnesium citrate or disodium carbonate. In some embodiments, the powder composition comprises a pharmaceutically acceptable diluents, such as sucrose, dextrose, mannitol, xylitol, or lactose.

[00739] Powder compositions of the inventions may be placed in sachets or bottles for contemporaneous dissolution or for short term storage in liquid form (e.g. 7 days).

Gummy Candies

[00740] The gummy candies of the invention may be prepared according to techniques well-known in the art of pharmacy.

[00741] Traditional gummy candy is made from a gelatin base. Gelatin gives the candy its elasticity, the desired chewy consistency, and a longer shelf life. In some embodiments, the gummy candy pharmaceutical composition of the invention includes a binding agent, a sweetener, and an active ingredient.

[00742] In some embodiments, the binding agent is a pectin gel, gelatin, food starch, or any combination thereof.

[00743] In some embodiments, the gummy candy comprises sweeteners, a binding agent, natural and/or artificial flavors and colors and preservatives. In some embodiments, the

gummy candy comprises glucose syrup, natural cane juice, gelatin, citric acid, lactic acid, natural colors, natural flavors, fractionated coconut oil, and carnauba wax.

Liquid Dosage Forms

[00744] The pharmaceutical liquid dosage forms of the invention may be prepared according to techniques well-known in the art of pharmacy.

[00745] A solution refers to a liquid pharmaceutical formulation wherein the active ingredient is dissolved in the liquid. Pharmaceutical solutions of the invention include syrups and elixirs. A suspension refers to a liquid pharmaceutical formulation wherein the active ingredient is in a precipitate in the liquid.

[00746] In a liquid dosage form, it is desirable to have a particular pH and/or to be maintained within a specific pH range. In order to control the pH, a suitable buffer system can be used. In addition, the buffer system should have sufficient capacity to maintain the desired pH range. Examples of the buffer system useful in the present invention include but are not limited to, citrate buffers, phosphate buffers, or any other suitable buffer known in the art. Preferably the buffer system include sodium citrate, potassium citrate, sodium bicarbonate, potassium bicarbonate, sodium dihydrogen phosphate and potassium dihydrogen phosphate, etc. The concentration of the buffer system in the final suspension varies according to factors such as the strength of the buffer system and the pH/pH ranges required for the liquid dosage form. In one embodiment, the concentration is within the range of 0.005 to 0.5 w/v % in the final liquid dosage form.

[00747] The pharmaceutical composition comprising the liquid dosage form of the present invention can also include a suspending/stabilizing agent to prevent settling of the active material. Over time the settling could lead to caking of the active to the inside walls of the product pack, leading to difficulties with redispersion and accurate dispensing. Suitable stabilizing agents include but are not limited to, the polysaccharide stabilizers such as xanthan, guar and tragacanth gums as well as the cellulose derivatives HPMC (hydroxypropyl methylcellulose), methyl cellulose and Avicel RC-591 (microcrystalline cellulose/sodium carboxymethyl cellulose). In another embodiment, polyvinylpyrrolidone (PVP) can also be used as a stabilizing agent.

[00748] In addition to the aforementioned components, the ASBTI oral suspension form can also optionally contain other excipients commonly found in pharmaceutical compositions such as alternative solvents, taste-masking agents, antioxidants, fillers, acidifiers, enzyme

inhibitors and other components as described in Handbook of Pharmaceutical Excipients, Rowe et al., Eds., 4th Edition, Pharmaceutical Press (2003), which is hereby incorporated by reference in its entirety for all purposes.

[00749] Addition of an alternative solvent may help increase solubility of an active ingredient in the liquid dosage form, and consequently the absorption and bioavailability inside the body of a subject. Preferably the alternative solvents include methanol, ethanol or propylene glycol and the like.

[00750] In another aspect, the present invention provides a process for preparing the liquid dosage form. The process comprises steps of bringing ASBTI or its pharmaceutically acceptable salts thereof into mixture with the components including glycerol or syrup or the mixture thereof, a preservative, a buffer system and a suspending/stabilizing agent, etc., in a liquid medium. In general, the liquid dosage form is prepared by uniformly and intimately mixing these various components in the liquid medium. For example, the components such as glycerol or syrup or the mixture thereof, a preservative, a buffer system and a suspending/stabilizing agent, etc., can be dissolved in water to form the aqueous solution, then the active ingredient can be then dispersed in the aqueous solution to form a suspension.

[00751] In some embodiments, the liquid dosage form provided herein can be in a volume of between about 5 ml to about 50 ml. In some embodiments, the liquid dosage form provided herein can be in a volume of between about 5 ml to about 40 ml. In some embodiments, the liquid dosage form provided herein can be in a volume of between about 5 ml to about 30 ml. In some embodiments, the liquid dosage form provided herein can be in a volume of between about 5 ml to about 20 ml. In some embodiments, the liquid dosage form provided herein can be in a volume of between about 10 ml to about 30 ml. In some embodiments, the liquid dosage form provided herein can be in a volume of about 20 ml. In some embodiments, the ASBTI can be in an amount ranging from about 0.001% to about 90% of the total volume. In some embodiments, the ASBTI can be in an amount ranging from about 0.01% to about 80% of the total volume. In some embodiments, the ASBTI can be in an amount ranging from about 0.1% to about 70% of the total volume. In some embodiments, the ASBTI can be in an amount ranging from about 1% to about 60% of the total volume. In some embodiments, the ASBTI can be in an amount ranging from about 1% to about 50% of the total volume. In some embodiments, the ASBTI can be in an amount ranging from about 1% to about 40% of the total volume. In some embodiments, the ASBTI can be in an amount ranging from about 1% to about 30% of the total volume. In some embodiments, the ASBTI can be in an amount

ranging from about 1% to about 20% of the total volume. In some embodiments, the ASBTI can be in an amount ranging from about 1% to about 10% of the total volume. In some embodiments, the ASBTI can be in an amount ranging from about 5% to about 70% of the total volume. In some embodiments, the ASBTI can be in an amount ranging from about 5% to about 60% of the total volume. In some embodiments, the ASBTI can be in an amount ranging from about 5% to about 50% of the total volume. In some embodiments, the ASBTI can be in an amount ranging from about 5% to about 40% of the total volume. In some embodiments, the ASBTI can be in an amount ranging from about 5% to about 30% of the total volume. In some embodiments, the ASBTI can be in an amount ranging from about 5% to about 20% of the total volume. In some embodiments, the ASBTI can be in an amount ranging from about 5% to about 10% of the total volume. In some embodiments, the ASBTI can be in an amount ranging from about 10% to about 50% of the total volume. In some embodiments, the ASBTI can be in an amount ranging from about 10% to about 40% of the total volume. In some embodiments, the ASBTI can be in an amount ranging from about 10% to about 30% of the total volume. In some embodiments, the ASBTI can be in an amount ranging from about 10% to about 20% of the total volume. In one embodiment, the resulted liquid dosage form can be in a liquid volume of 10 ml to 30 ml, preferably 20 ml, and the active ingredient can be in an amount ranging from about 0.001 mg/ml to about 16 mg/ml, or from about 0.025 mg/ml to about 8 mg/ml, or from about 0.1 mg/ml to about 4 mg/ml, or about 0.25 mg/ml, or about 0.5 mg/ml, or about 1 mg/ml, or about 2 mg/ml, or about 4 mg/ml, or about 5 mg/ml, or about 8 mg/ml, or about 10 mg/ml, or about 12 mg/ml, or about 14 mg/ml or about 16 mg/ml.

Bile Acid Sequestrant

[00752] In certain embodiments, an oral formulation for use in any method described herein is, e.g., an ASBTI in association with a labile bile acid sequestrant. A labile bile acid sequestrant is a bile acid sequestrant with a labile affinity for bile acids. In certain embodiments, a bile acid sequestrant described herein is an agent that sequesters (e.g., absorbs or is charged with) bile acid, and/or the salts thereof.

[00753] In specific embodiments, the labile bile acid sequestrant is an agent that sequesters (e.g., absorbs or is charged with) bile acid, and/or the salts thereof, and releases at least a portion of the absorbed or charged bile acid, and/or salts thereof in the distal gastrointestinal tract (e.g., the colon, ascending colon, sigmoid colon, distal colon, rectum, or any

combination thereof). In certain embodiments, the labile bile acid sequestrant is an enzyme dependent bile acid sequestrant. In specific embodiments, the enzyme is a bacterial enzyme. In some embodiments, the enzyme is a bacterial enzyme found in high concentration in human colon or rectum relative to the concentration found in the small intestine. Examples of micro-flora activated systems include dosage forms comprising pectin, galactomannan, and/or Azo hydrogels and/or glycoside conjugates (e.g., conjugates of D-galactoside, β-D-xylopyranoside or the like) of the active agent. Examples of gastrointestinal micro-flora enzymes include bacterial glycosidases such as, for example, D-galactosidase, β-D-glucosidase, α-L-arabinofuranosidase, β-D-xylopyranosidase or the like. In some embodiments, the labile bile acid sequestrant is a time dependent bile acid sequestrant (i.e., the bile acid sequesters the bile acid and/or salts thereof and after a time releases at least a portion of the bile acid and/or salts thereof). In some embodiments, a time dependent bile acid sequestrant is an agent that degrades in an aqueous environment over time. In certain embodiments, a labile bile acid sequestrant described herein is a bile acid sequestrant that has a low affinity for bile acid and/or salts thereof, thereby allowing the bile acid sequestrant to continue to sequester bile acid and/or salts thereof in an environ where the bile acids/salts and/or salts thereof are present in high concentration and release them in an environ wherein bile acids/salts and/or salts thereof are present in a lower relative concentration. In some embodiments, the labile bile acid sequestrant has a high affinity for a primary bile acid and a low affinity for a secondary bile acid, allowing the bile acid sequestrant to sequester a primary bile acid or salt thereof and subsequently release a secondary bile acid or salt thereof as the primary bile acid or salt thereof is converted (e.g., metabolized) to the secondary bile acid or salt thereof. In some embodiments, the labile bile acid sequestrant is a pH dependent bile acid sequestrant. In some embodiments, the pH dependent bile acid sequestrant has a high affinity for bile acid at a pH of 6 or below and a low affinity for bile acid at a pH above 6. In certain embodiments, the pH dependent bile acid sequestrant degrades at a pH above 6.

[00754] In some embodiments, labile bile acid sequestrants described herein include any compound, e.g., a macro-structured compound, that can sequester bile acids/salts and/or salts thereof through any suitable mechanism. For example, in certain embodiments, bile acid sequestrants sequester bile acids/salts and/or salts thereof through ionic interactions, polar interactions, static interactions, hydrophobic interactions, lipophilic interactions, hydrophilic interactions, steric interactions, or the like. In certain embodiments, macrostructured compounds sequester bile acids/salts and/or sequestrants by trapping the bile acids/salts

and/or salts thereof in pockets of the macrostructured compounds and, optionally, other interactions, such as those described above. In some embodiments, bile acid sequestrants (e.g., labile bile acid sequestrants) include, by way of non-limiting example, lignin, modified lignin, polymers, polycationic polymers and copolymers, polymers and/or copolymers comprising anyone one or more of N-alkenyl-N-alkylaminc 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; or a combination thereof, or any combination thereof.

Covalent Linkage of the Drug with a Carrier

[00755] In some embodiments, strategies used for colon targeted delivery include, by way of non-limiting example, covalent linkage of the ASBTI or other compounds described herein to a carrier, coating the dosage form with a pH-sensitive polymer for delivery upon reaching the pH environment of the colon, using redox sensitive polymers, using a time released formulation, utilizing coatings that are specifically degraded by colonic bacteria, using bioadhesive system and using osmotically controlled drug delivery systems.

[00756] In certain embodiments of such oral administration of a composition containing an ASBTI or other compounds described herein involves covalent linking to a carrier wherein upon oral administration the linked moiety remains intact in the stomach and small intestine. Upon entering the colon, the covalent linkage is broken by the change in pH, enzymes, and/or degradation by intestinal microflora. In certain embodiments, the covalent linkage between the ASBTI and the carrier includes, by way of non-limiting example, azo linkage, glycoside conjugates, glucuronide conjugates, cyclodextrin conjugates, dextran conjugates, and amino-acid conjugates (high hydrophilicity and long chain length of the carrier amino acid).

Coating with Polymers: pH-Sensitive Polymers

[00757] In some embodiments, the oral dosage forms described herein are coated with an enteric coating to facilitate the delivery of an ASBTI or other compounds described herein to the colon and/or rectum. In certain embodiments, an enteric coating is one that remains intact in the low pH environment of the stomach, but readily dissolved when the optimum dissolution pH of the particular coating is reached which depends upon the chemical composition of the enteric coating. The thickness of the coating will depend upon the solubility characteristics of the coating material. In certain embodiments, the coating

thicknesses used in such formulations described herein range from about 25 μm to about 200 μm.

[00758] In certain embodiments, the compositions or formulations described herein are coated such that an ASBTI or other compounds described herein of the composition or formulation is delivered to the colon and/or rectum without absorbing at the upper part of the intestine. In a specific embodiment, specific delivery to the colon and/or rectum is achieved by coating of the dosage form with polymers that degrade only in the pH environment of the colon. In alternative embodiments, the composition is coated with an enteric coat that dissolves in the pH of the intestines and an outer layer matrix that slowly erodes in the intestine. In some of such embodiments, the matrix slowly erodes until only a core composition comprising an enteroendocrine peptide secretion enhancing agent (and, in some embodiments, an absorption inhibitor of the agent) is left and the core is delivered to the colon and/or rectum.

[00759] In certain embodiments, pH-dependent systems exploit the progressively increasing pH along the human gastrointestinal tract (GIT) from the stomach (pH 1-2 which increases to 4 during digestion), small intestine (pH 6-7) at the site of digestion and it to 7-8 in the distal ileum. In certain embodiments, dosage forms for oral administration of the compositions described herein are coated with pH-sensitive polymer(s) to provide delayed release and protect the enteroendocrine peptide secretion enhancing agents from gastric fluid. In certain embodiments, such polymers are be able to withstand the lower pH values of the stomach and of the proximal part of the small intestine but disintegrate at the neutral or slightly alkaline pH of the terminal ileum and/or ileocecal junction. Thus, in certain embodiments, provided herein is an oral dosage form comprising a coating, the coating comprising a pH-sensitive polymer. In some embodiments, the polymers used for colon and/or rectum targeting include, by way of non-limiting example, methacrylic acid copolymers, methacrylic acid and methyl methacrylate copolymers, Eudragit L100, Eudragit S100, Eudragit L-30D, Eudragit FS-30D, Eudragit L100-55, polyvinylacetate phthalate, hyrdoxypropyl ethyl cellulose phthalate, hyrdoxypropyl methyl cellulose phthalate 50, hyrdoxypropyl methyl cellulose phthalate 55, cellulose acetate trimelliate, cellulose acetate phthalate and combinations thereof.

[00760] In certain embodiments, oral dosage forms suitable for delivery to the colon and/or rectum comprise a coating that has a biodegradable and/or bacteria degradable polymer or polymers that are degraded by the microflora (bacteria) in the colon. In such biodegradable systems suitable polymers include, by way of non-limiting example, azo polymers, linear-

type-segmented polyurethanes containing azo groups, polygalactomannans, pectin, glutaraldehyde crosslinked dextran, polysaccharides, amylose, guar gum, pectin, chitosan, inulin, cyclodextrins, chondroitin sulphate, dextrans, locust bean gum, chondroitin sulphate, chitosan, poly (-caprolactone), polylactic acid and poly(lactic-co-glycolic acid).

[00761] In certain embodiments of such oral administration of compositions containing one or more ASBTIs or other compounds described herein, the compositions are delivered to the colon without absorbing at the upper part of the intestine by coating of the dosage forms with redox sensitive polymers that are degraded by the microflora (bacteria) in the colon. In such biodegradable systems such polymers include, by way of non-limiting example, redox-sensitive polymers containing an azo and/or a disulfide linkage in the backbone.

[00762] In some embodiments, compositions formulated for delivery to the colon and/or rectum are formulated for time-release. In some embodiments, time release formulations resist the acidic environment of the stomach, thereby delaying the release of the enteroendocrine peptide secretion enhancing agents until the dosage form enters the colon and/or rectum.

[00763] In certain embodiments the time released formulations described herein comprise a capsule (comprising an enteroendocrine peptide secretion enhancing agent and an optional absorption inhibitor) with hydrogel plug. In certain embodiments, the capsule and hydrogel plug are covered by a water-soluble cap and the whole unit is coated with an enteric polymer. When the capsule enters the small intestine the enteric coating dissolves and the hydrogels plug swells and dislodges from the capsule after a period of time and the composition is released from the capsule. The amount of hydrogel is used to adjust the period of time to the release the contents.

[00764] In some embodiments, provided herein is an oral dosage form comprising a multi-layered coat, wherein the coat comprises different layers of polymers having different pH-sensitivities. As the coated dosage form moves along GIT the different layers dissolve depending on the pH encountered. Polymers used in such formulations include, by way of non-limiting example, polymethacrylates with appropriate pH dissolution characteristics, Eudragit® RL and Eudragit®RS (inner layer), and Eudragit® FS (outer layer). In other embodiments the dosage form is an enteric coated tablets having an outer shell of hydroxypropylcellulose or hydroxypropylmethylcellulose acetate succinate (HPMCAS).

[00765] In some embodiments, provided herein is an oral dosage form that comprises coat with cellulose butyrate phthalate, cellulose hydrogen phthalate, cellulose proprionate

phthalate, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate, dioxypropyl methylcellulose succinate, carboxymethyl ethylcellulose, hydroxypropyl methylcellulose acetate succinate, polymers and copolymers formed from acrylic acid, methacrylic acid, and combinations thereof.

Combination Therapy

[00766] In some embodiments, the methods provided herein comprise administering a compound (e.g., an ASBTI) or composition described herein in combination with one or more additional agents. In some embodiments, the present invention also provides a composition comprising a compound (e.g., an ASBTI) with one or more additional agents.

Fat Soluble Vitamins

[00767] In some embodiments, the methods provided herein further comprise administering one or more vitamins. In some embodiments, the vitamin is vitamin A, B1, B2, B3, B5, B6, B7, B9, B12, C, D, E, K, folic acid, pantothenic acid, niacin, riboflavin, thiamine, retinol, beta carotene, pyridoxine, ascorbic acid, cholecalciferol, cyanocobalamin, tocopherols, phylloquinone, menaquinone.

[00768] In some embodiments, the vitamin is a fat soluble vitamin such as vitamin A, D, E, K, retinol, beta carotene, cholecalciferol, tocopherols, phylloquinone. In a preferred embodiment, the fat soluble vitamin is tocopherol polyethylene glycol succinate (TPGS).

Partial External Biliary Diversion (PEBD)

[00769] In some embodiments, the methods provided herein further comprise using partial external biliary diversion as a treatment for patients who have not yet developed cirrhosis. This treatment helps reduce the circulation of bile acids/salts in the liver in order to reduce complications and prevent the need for early transplantation in many patients.

[00770] This surgical technique involves isolating a segment of intestine 10 cm long for use as a biliary conduit (a channel for the passage of bile) from the rest of the intestine. One end of the conduit is attached to the gallbladder and the other end is brought out to the skin to form a stoma (a surgically constructed opening to permit the passage of waste). Partial external biliary diversion may be used for patients who are unresponsive to all medical therapy, especially older, larger patients. This procedure may not be of help to young patients such as infants. Partial external biliary diversion may decrease the intensity of the itching and abnormally low levels of cholesterol in the blood.

ASBTIs and PPAR agonists

[00771] In various embodiments, the present invention provides methods of use of combinations of ASBTIs with PPAR (peroxisome proliferator-activated receptor) agonists. In various embodiments, the PPAR agonist is a fibrate drug. In some embodiments, the fibrate drug is clofibrate, gemfibrozil, ciprofibrate, benzafibrate, fenofibrate, or various combinations thereof. In various embodiments, the PPAR agonist is aleglitazar, muraglitazar, tesaglitazar, saroglitazar, GW501516, GW-9662, a thiazolidinedione (TZD), a NSAID (e.g., IBUPROFEN), an indole, or various combinations thereof.

ASBTIs and FXR drugs

[00772] In various embodiments, the present invention provides methods of use of combinations of ASBTIs with farnesoid X receptor (FXR) targeting drugs. In various embodiments, the FXR targeting drug is avermectin B1a, bepridil, fluticasone propionate, GW4064, gliquidone, nicardipine, triclosan, CDCA, ivermectin, chlorotrianisene, tribenoside, mometasone furoate, miconazole, amiodarone, butoconazolee, bromocryptine mesylate, pizotifen malate, or various combinations thereof.

ASBTI and Ursodiol

[00773] In some embodiments, an ASBTI is administered in combination with ursodiol or ursodeoxycholic acid, chenodeoxycholic acid, cholic acid, taurocholic acid, ursocholic acid, glycocholic acid, glycodeoxycholic acid, taurodeoxycholic acid, taurocholate, glycochenodeoxycholic acid, tauroursodeoxycholic acid. In some embodiments, an increase in the concentration of bile acids/salts in the distal intestine induces intestinal regeneration, attenuating intestinal injury, reducing bacterial translocation, inhibiting the release of free radical oxygen, inhibiting production of proinflammatory cytokines, or any combination thereof or any combination thereof.

[00774] In certain embodiments, the patient is administered ursodiol at a daily dose of about or of at least about 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 36 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1,000 mg, 1,250 mg, 1,500 mg, 1,750 mg, 2,000 mg, 2,250 mg, 2,500 mg, 2,750 mg, or 3,000 mg. In certain embodiments, the patient is administered ursodiol at a daily dose of about or of no more than about 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 36 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80

mg, 85 mg, 90 mg, 95 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1,000 mg, 1,250 mg, 1,500 mg, 1,750 mg, 2,000 mg, 2,250 mg, 2,500 mg, 2,750 mg, 3,000 mg, or 3,500 mg. In various embodiments, the patient is administered ursodiol at a daily dose of about or of at least about 3 mg to about 300 mg, about 30 mg to about 250 mg, from about 36 mg to about 200 mg, from about 10 mg to about 3000 mg, from about 1000 mg to about 2000 mg, or from about 1500 to about 1900 mg.

[00775] In various embodiments the ursodiol is administered as a tablet. In various embodiments, the ursodiol is administered as a suspension. In various embodiments, the concentration of ursodiol in the suspension is from about 10 mg/mL to about 200 mg/mL, from about 50 mg/mL to about 150 mg/mL, from about 10 mg/mL to about 500 mg/mL, or from about 40 mg/mL to about 60 mg/mL. In various embodiments, the concentration of ursodiol in suspension is about or is at least about 20 mg/mL, 25 mg/mL , 30 mg/mL, 35 mg/mL, 40 mg/mL, 45 mg/mL, 50 mg/mL, 55 mg/mL, 60 mg/mL, 65 mg/mL, 70 mg/mL, 75 mg/mL, or 80 mg/mL. In various embodiments, the concentration of ursodiol in suspension is no more than about 25 mg/mL , 30 mg/mL, 35 mg/mL, 40 mg/mL, 45 mg/mL, 50 mg/mL, 55 mg/mL, 60 mg/mL, 65 mg/mL, 70 mg/mL, 75 mg/mL, 80 mg/mL, or 85 mg/mL.

[00776] An ASBTI and a second active ingredient are used such that the combination is present in a therapeutically effective amount. That therapeutically effective amount arises from the use of a combination of an ASBTI and the other active ingredient (e.g., ursodiol) wherein each is used in a therapeutically effective amount, or by virtue of additive or synergistic effects arising from the combined use, each can also be used in a subclinical therapeutically effective amount, i.e., an amount that, if used alone, provides for reduced effectiveness for the therapeutic purposes noted herein, provided that the combined use is therapeutically effective. In some embodiments, the use of a combination of an ASBTI and any other active ingredient as described herein encompasses combinations where the ASBTI or the other active ingredient is present in a therapeutically effective amount, and the other is present in a subclinical therapeutically effective amount, provided that the combined use is therapeutically effective owing to their additive or synergistic effects. As used herein, the term “additive effect” describes the combined effect of two (or more) pharmaceutically active agents that is equal to the sum of the effect of each agent given alone. A syngergistic effect is one in which the combined effect of two (or more) pharmaceutically active agents is greater than the sum of the effect of each agent given alone. Any suitable combination of an ASBTI

with one or more of the aforementioned other active ingredients and optionally with one or more other pharmacologically active substances is contemplated as being within the scope of the methods described herein.

[00777] In some embodiments, the particular choice of compounds depends upon the diagnosis of the attending physicians and their judgment of the condition of the individual and the appropriate treatment protocol. The compounds are optionally administered concurrently (e.g., simultaneously, essentially simultaneously or within the same treatment protocol) or sequentially, depending upon the nature of the disease, disorder, or condition, the condition of the individual, and the actual choice of compounds used. In certain instances, the determination of the order of administration, and the number of repetitions of administration of each therapeutic agent during a treatment protocol, is based on an evaluation of the disease being treated and the condition of the individual.

[00778] In some embodiments, therapeutically-effective dosages vary when the drugs are used in treatment combinations. Methods for experimentally determining therapeutically-effective dosages of drugs and other agents for use in combination treatment regimens are described in the literature.

[00779] In some embodiments of the combination therapies described herein, dosages of the co-administered compounds vary depending on the type of co-drug employed, on the specific drug employed, on the disease or condition being treated and so forth. In addition, when co-administered with one or more biologically active agents, the compound provided herein is optionally administered either simultaneously with the biologically active agent(s), or sequentially. In certain instances, if administered sequentially, the attending physician will decide on the appropriate sequence of therapeutic compound described herein in combination with the additional therapeutic agent.

[00780] The multiple therapeutic agents (at least one of which is a therapeutic compound described herein) are optionally administered in any order or even simultaneously. If simultaneously, the multiple therapeutic agents are optionally provided in a single, unified form, or in multiple forms (by way of example only, either as a single pill or as two separate pills). In certain instances, one of the therapeutic agents is optionally given in multiple doses. In other instances, both are optionally given as multiple doses. If not simultaneous, the timing between the multiple doses is any suitable timing; e.g, from more than zero weeks to less than four weeks. In addition, the combination methods, compositions and formulations are not to

be limited to the use of only two agents; the use of multiple therapeutic combinations are also envisioned (including two or more compounds described herein).

[00781] In certain embodiments, a dosage regimen to treat, prevent, or ameliorate the condition(s) for which relief is sought, is modified in accordance with a variety of factors. These factors include the disorder from which the subject suffers, as well as the age, weight, sex, diet, and medical condition of the subject. Thus, in various embodiments, the dosage regimen actually employed varies and deviates from the dosage regimens set forth herein.

[00782] In some embodiments, the pharmaceutical agents which make up the combination therapy described herein are provided in a combined dosage form or in separate dosage forms intended for substantially simultaneous administration. In certain embodiments, the pharmaceutical agents that make up the combination therapy are administered sequentially, with either therapeutic compound being administered by a regimen calling for two-step administration. In some embodiments, two-step administration regimen calls for sequential administration of the active agents or spaced-apart administration of the separate active agents. In certain embodiments, the time period between the multiple administration steps varies, by way of non-limiting example, from a few minutes to several hours, depending upon the properties of each pharmaceutical agent, such as potency, solubility, bioavailability, plasma half-life and kinetic profile of the pharmaceutical agent.

[00783] In certain embodiments, provided herein are combination therapies. In certain embodiments, the compositions described herein comprise an additional therapeutic agent. In some embodiments, the methods described herein comprise administration of a second dosage form comprising an additional therapeutic agent. In certain embodiments, combination therapies the compositions described herein are administered as part of a regimen. Therefore, additional therapeutic agents and/or additional pharmaceutical dosage form can be applied to a patient either directly or indirectly, and concomitantly or sequentially, with the compositions and formulations described herein.

Kits

[00784] In another aspect, provided herein are kits containing a device for rectal administration pre-filled a pharmaceutical composition described herein. In certain embodiments, kits contain a device for oral administration and a pharmaceutical composition as described herein. In certain embodiments the kits include prefilled sachet or bottle for oral administration, while in other embodiments the kits include prefilled bags for administration

of rectal gels. In certain embodiments the kits include prefilled syringes for administration of oral enemas, while in other embodiments the kits include prefilled syringes for administration of rectal gels. In certain embodiments the kits include prefilled pressurized cans for administration of rectal foams.

Release in Distal Ileum and/or Colon

[00785] In certain embodiments, a dosage form comprises a matrix (e.g., a matrix comprising hypermellose) that allows for controlled release of an active agent in the distal jejunum, proximal ileum, distal ileum and/or the colon. In some embodiments, a dosage form comprises a polymer that is pH sensitive (e.g., a MMX™ matrix from Cosmo Pharmaceuticals) and allows for controlled release of an active agent in the ileum and/or the colon. Examples of such pH sensitive polymers suitable for controlled release include and are not limited to polyacrylic polymers (e.g., anionic polymers of methacrylic acid and/or methacrylic acid esters, e.g., Carbopol® polymers) that comprise acidic groups (e.g., —COOH, —SO_3H) and swell in basic pH of the intestine (e.g., pH of about 7 to about 8). In some embodiments, a dosage form suitable for controlled release in the distal ileum comprises microparticulate active agent (e.g., micronized active agent). In some embodiments, a non-enzymatically degrading poly(dl-lactide-co-glycolide) (PLGA) core is suitable for delivery of an ASBTI to the distal ileum. In some embodiments, a dosage form comprising an ASBTI is coated with an enteric polymer (e.g., Eudragit® S-100, cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethylcellulose phthalate, anionic polymers of methacrylic acid, methacrylic acid esters or the like) for site specific delivery to the ileum and/or the colon. In some embodiments, bacterially activated systems are suitable for targeted delivery to the ileum. Examples of micro-flora activated systems include dosage forms comprising pectin, galactomannan, and/or Azo hydrogels and/or glycoside conjugates (e.g., conjugates of D-galactoside, β-D-xylopyranoside or the like) of the active agent. Examples of gastrointestinal micro-flora enzymes include bacterial glycosidases such as, for example, D-galactosidase, β-D-glucosidase, α-L-arabinofuranosidase, β-D-xylopyranosidase or the like.

[00786] The pharmaceutical solid dosage forms described herein optionally include an additional therapeutic compound described herein and one or more pharmaceutically acceptable additives such as a compatible carrier, binder, filling agent, suspending agent, flavoring agent, sweetening agent, disintegrating agent, dispersing agent, surfactant,

lubricant, colorant, diluent, solubilizer, moistening agent, plasticizer, stabilizer, penetration enhancer, wetting agent, anti-foaming agent, antioxidant, preservative, or one or more combination thereof. In some aspects, using standard coating procedures, such as those described in *Remington's Pharmaceutical Sciences,* 20th Edition (2000), a film coating is provided around the formulation of the ASBTI. In one embodiment, a compound described herein is in the form of a particle and some or all of the particles of the compound are coated. In certain embodiments, some or all of the particles of a compound described herein are microencapsulated. In some embodiments, the particles of the compound described herein are not microencapsulated and are uncoated.

[00787] An ASBT inhibitor may be used in the preparation of medicaments for the prophylactic and/or therapeutic treatment of cholestasis or a cholestatic liver disease. A method for treating any of the diseases or conditions described herein in an individual in need of such treatment, may involve administration of pharmaceutical compositions containing at least one ASBT inhibitor described herein, or a pharmaceutically acceptable salt, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof, in therapeutically effective amounts to said individual.

EXAMPLES

[00788] The following examples are provided to further describe some of the embodiments disclosed herein. The examples are intended to illustrate, not to limit, the disclosed embodiments.

Example 1. Phase 2 open-label efficacy and safety study of the apical sodium-dependent bile acid transporter inhibitor maralixibat in children with progressive familial intrahepatic cholestasis (INDIGO clinical study)

[00789] The dosing regimen used in the INDIGO clinical study is summarized in Fig. 2. In addition to the doses indicated in Fig. 2, some patients were administered a dose of 280 μg/kg twice a day (BID) after initially being administered a dose of 280 μg/kg daily (QD). Dosing was escalated up to 280 μg/kg QD over a period of 8 weeks.

[00790] Key inclusion criteria for the INDIGO clinical study were the following: 1) aged 1-18 years; 2) clinically diagnosed with PFIC; 3) two mutant *ABCB11* or *ATB8B1* alleles. Key exclusion criteria for the INDIGO clinical study were the following: 1) surgically disrupted enterohepatic circulation; 2) liver transplant; 3) decompensated cirrhosis.

[00791] The following cholestasis biomarkers were monitored in the INDIGO clinical study, among others: serum bile acid concentration (sBA); serum alanine aminotransferase (ALT) concentration; serum aspartate aminotransferase (AST) concentration; serum bilirubin concentration; and serum 7αC4 concentration. Fecal bile acid (fBA) concentration was also measured. Severity of pruritus was assessed throughout the INDIGO clinical study using observer-reported itch-reported outcome (ITCHRO(OBS)) weekly average score (parent-rated e-diary) and clinician scratch scale (CSS) score (investigator-rated). Patients were also administered a health-related quality of life (HRQoL) assessment throughout the INDIGO clinical study. The HRQoL used was the PEDIATRIC QUALITY OF LIFE INVENTORY (PedsQL). Multi-parameter response was defined by a greater than 70% reduction or normalization in sBA concentration and a greater than 1.0 reduction or lower than 1.0 in ITCHRO(OBS) score.

[00792] Table 1 provides a summary of demographics and baseline health-related parameters for participants in the INDIGO clinical study. Of 25 participants suffering PFIC 2, 19 participants had non-truncating *ABCB11* mutations (classified as mild or moderate) and 6 participants had truncating *ABCB11* mutations, see Tables 2-3 and 5. 29 participants reached week 48, see Table 4. Mild PFIC 2 was defined as PFIC 2 resulting from a E297G or a D482G mutation to the *ABCB11* gene while moderate PFIC 2 was defined as PFIC 2 resulting from an *ABCB11* gene comprising missense mutations but not comprising a E297G or a D482G mutation, see Table 3. Of the 19 participants having non-truncating *ABCB11* mutations, 7 suffered mild PFIC 2 and 12 suffered moderate PFIC 2, see Table 3 and Table 5. One patient (1 of 7 mild PFIC 2 patients) suffering mild PFIC 2 was a multi-parameter responder in the INDIGO clinical study at a dose of 280 µg/kg QD, see Tables 3, 4, and 6. One patient (1 of 12 moderate PFIC 2 patients) suffering moderate PFIC 2 only demonstrated responsiveness (high-dose responder) after being administered a dose of maralixibat of 280 µg/kg twice daily (discussed further below), see Tables 3, 4, and 8. Five patients (5 of 12 moderate PFIC 2 patients) were responders in the INDIGO clinical study at a dose of 280 µg/kg/day by week 48 of the INDIGO clinical study, see Tables 3-9. All PFIC 1 patients and all patients harboring a truncating *ABCB11* mutation were not multi-parameter responders in the INDIGO clinical study, see Tables 3, 5 and Fig. 5.

[00793] Patients indicated as having no response in Table 3 demonstrated no response within the times and at the maximum dosages provided in Table 6. Patients showing no

response, therefore, may have demonstrated a response if administered maralixibat at a higher dose or for a longer time duration.

Table 1: Baseline disease characteristics and demographics for participants in the INDIGO clinical study

Patient Characteristics

N=33	PFIC1, n=8 FIC1 def.	PFIC2, n=25 BSEP def.
Median Age (range), year	2.0 (1-7)	4.0 (1-13)
Boys, n (%)	6 (75)	8 (32)
White, n (%)	6 (75)	20(80)
Serum bile acid (range) µmol/L	261.9 (159.8-423.5)	381.0 (34.4-602.1)
Mean (SD) z=scores		
Height	-2.96 (1.47)	-1.29 (0.98)
Weight	-2.70 (2.82)	-0.63 (0.88)

Table 2: Genetic status of participants in the INDIGO clinical study having PFIC 2

BSEP Genetic Status

	Participants (n)
Non-truncating (mild/moderate)	19
Truncating	6

Table 3: *ABCB11* genotypes, PFIC 2 classifications, and observed responses for PFIC 2 participants in the INDIGO clinical study

Subject ID	**Mutation 1**		**Mutation 2**			
	cDNA	**Protein**	**cDNA**	**Protein**	**Classification**	**Response**
001051-J-D	c.149T>C	Leu50Ser	c.3667G>A	Glu1223Lys	Moderate	No reponse
001053-M-E	c.890A>G	Glu297Gly	c.890A>G	Glu297Gly	Mild	No reponse
001054-LOA	c.2495G>A	Arg832His	c.2842C>T	Arg948Cys	Moderate	Rapid complete response
001055-H-B	c. 2611-2 A>T	Splice site	c. 2611-2 A>T	Splice site	Severe	No reponse
001057-W-R	c.319T>C	Cys107Arg	c.319T>C	Cys107Arg	Moderate	No reponse
001060	c.319T>C	Cys107Arg	c.319T>C	Cys107Arg	Moderate	No reponse
002052-M-H	c.1145-1165del	p.Ala382_Ala388del	c.2787_2788insGAGAT	p.Lys930Glufs*79	Severe	No reponse
002053-E-B	c.499G>A	p.A167T	c.3457G>A	p.R1153S	Moderate	No reponse
002054-KRD	c.149T>C	p.L50S	c.890A>G	p.E297G	Mild	No reponse
003052-R-C	c.890A>G	Glu297Gly	c.2012-8T>G	Splice site	Mild	No reponse

003053-A-J	c.890A>G	Glu297Gly	c.2842C>T	Arg948Cys	Mild	No reponse
013051-T-C	c.403G>A	E135K	c.1012-8T>G	Splice site	Moderate	No reponse
013052-JMC	c.1408C>T	p.R470*	c.3945delC	p.T1316Lfs*64	Severe	No reponse
014051	c.1460G>C	p.(Arg487Pro)	c.2944G>A	p.(Gly982Arg)	Moderate	No reponse
016051----	c.470A>G	p.Y157C	c.3892G>A	p.G1298R	Moderate	Rapid complete response
016052----	c.470A>G	p.Y157C	c.3892G>A	p.G1298R	Moderate	Rapid complete response
016053----	c.757G>A	Gly253Arg	c.1769A>G	Asp590Gly	Moderate	Good response
016054----	c.2783_2787dupGAGAT	Lys930Glufs*79	c.1769A>G	Asp590Gly	Moderate	No response until 560 reached
027051-T-S	c.3457C>T	Arg1153Cys	c.3476T>C	Val1159Ala	Moderate	Rapid complete response
027052-AJC	c.890A>G	Glu297Gly	c.3491delT	Val1164Glyfs7	Mild	No reponse
027053-VJB	c.890A>G	Glu297Gly	c.890A>G	Glu297Gly	Mild	No reponse
052051-S-C	c.1826_1827insCA	Ile610fs	c.1826_1827insCA	Ile610fs	Severe	No reponse

052052-S-M	c.1827_1828insCA	Ile610fs	c.1827_1828insCA	Ile610fs	Severe	No reponse
052054	c.1062T>A	Tyr354Ter	1052T>A	Tyr354Ter	Severe	No reponse
080051-L-M	c.1558A>T	p.(Arg520Ter)	c.1445A>G	p.Asp482Gly	Mild	>70% reduction in BAs

Table 4: Disposition of patients in the INDIGO study to week 48

Reached week 48, n	29
Efficacy data available, n	26
PFIC1	6
PFIC2	20
Maralixibat dose, n	
280 µg/kg/day	23
140 µg/kg/day	2
< 140 µg/kg/day[a]	1

[a]One patient receiving 280 µ/kg/day had a treatment interruption and was re-escalated at week 48

Table 5: Summary of subject PFIC genotype status for responders in the INDIGO clinical study

Subject Genotype Status	**Multi-parameter Responders**
Non-truncating BSEP (N=19)	7/19 (36.8%)
Mild (N=7)	1/7 (14.3%)
Moderate (N=12)	6/12 (50%)
Truncating BSEP (N=6)	0/6 (0%)

Table 6: Study duration and max dose for participants in the INDIGO clinical study

Subject ID	**Max dose**	**Study duration**
001051-J-D	280	72 weeks
001053-M-E	280	72 weeks
001054-LOA	280	1328 days
001055-H-B	280	124 weeks
001057-W-R	560	1247 days
001060	280	60 weeks
002052-M-H	280	86 weeks
002053-E-B	280	60 weeks

002054-KRD	280	72 weeks
003052-R-C	280	72 weeks
003053-A-J	560	1127 days
013051-T-C	280	60 weeks
013052-JMC	280	122 weeks
014051	280	60 weeks
016051----	280	1218 days
016052----	280	1218 days
016053----	560	1196 days
016054----	560	927 days
027051-T-S	280	1220 days
027052-AJC	280	72 weeks
027053-VJB	280	72 weeks
052051-S-C	280	72 weeks
052052-S-M	280	72 weeks
052054	280	72 weeks
080051-L-M	560	924 days

Table 7: Summary of efficacy measures at baseline and changes at week 48 of the INDIGO clinical study

sBA, µmol/L	ALT, UI/L	Total bilirubin, mg/dL	C4, ng/mL	ItchRO(Obs) score	PedsQL total score
Baseline, mean (range)					
352 (34, 602)	108 (13, 438)	2.9 (0.1, 15.1)	4.2 (0.1, 47.3)	2.3 (0.1, 3.8)	61.5 (18.1, 85.9)
Change from baseline to week 48, mean (95% CI)					

-32 (-110, +46)	-12 (-36, +13)	+0.8 (-0.1, +1.7)	+6.0 (-0.6, +12.5)	-1.0 (-1.4, -0.6)	+8.2 (+0.7, +15.6)

Table 8: Summary of responders observed in PFIC patients that participated in the INDIGO clinical study (n=6) by week 48

Diagnosis, n	
PFIC1 *(ATP8B1* mutation)	0
PFIC2 *(ABCB11* mutation)	6
Reached week 48, n	6
Maralixibat dose, n	
280 µg/kg/day	6

Table 9: Overview of responses observed in responders in the INDIGO clinical study (n=6) by week 48

sBA levels, n	
Normalized (±≤8.5 µmol/L)	4
Reduced by ≥70% or ≥80% from baseline	2
ItchRO score, n	
Zero (no pruritus)	2
Improved by ≥1.0 points from baseline	4

[00794] Therefore, in view of the above observations, patient responsiveness to administration of maralixibat correlated with patient genotype. In particular, the INDIGO clinical study revealed the surprising result that only patients suffering PFIC 2 caused by a non-truncating *ABCB11* gene mutation were responders to administration of maralixibat. Additionally, it was unexpectedly found that moderate PFIC 2 patients were more likely to show a response at 280 µg/kg/day of maralixibat than mild PFIC 2 patients, see Tables 3 and 5-6.

[00795] The six patients demonstrating a response at 280 µg/kg/day of maralixibat (low-dose responders) demonstrated a decrease in sBA concentration, serum ALT concentration, serum bilirubin concentration, ITCHRO(OBS) score, and PEDSQL score and increase in serum 7αC4 (C4) concentration by week 48 of the INDIGO clinical study, see Table 7. Two of the low-dose responders demonstrated a reduction in sBA from baseline of over 70% or over 80%, see Table 9. Four of the low-dose responders demonstrated a normalization in sBA, see Table 9. A detailed overview of each of the six low-dose responders to maralixibat administration is provided as Fig. 3. All low-dose responders demonstrated an increase in C4

levels of at least 2.5-fold relative to baseline within 13 weeks of first administration of maralixibat in the INDIGO clinical study. All low-dose responders demonstrated establishment of normalized or only mildly elevated concentrations of serum ALT, AST, and bilirubin concentrations over time (e.g., within 2-6 months of first administration of maralixibat) in the INDIGO clinical study.

[00796] Gastrointestinal infections were found to interfere with of the treatment effect of maralixibat in PFIC 2, see Figs. 3D and 3E. Therefore, gastrointestinal infections may cause otherwise responsive patients to appear non-responsive to administration of maralixibat.

[00797] Three patients that did not demonstrate a response at a dose of 280 µg/kg/day of maralixibat non-truncating PFIC 2 were administered 560 µg/kg/day of maralixibat and one (mentioned above) responded at the higher dose, see Tables 3 and 6.

[00798] The low-dose responders demonstrated 7αC4 concentrations at 48 weeks that were 14 x baseline (range, 3-43). Non-responder 7αC4 concentrations were 1.8 x baseline (range, 0.5-6) at 48 weeks. This demonstrates a correlation between response and increased BA synthesis. The mean change from baseline at week 48 in the ratio of 7αC4 concentration to sBA concentration (7αC4:sBA) for the low-dose responders was 1388 times baseline ratio (range, 5-3982), whereas the ratio was 1.9 times baseline ratio (range, 0.43-12) in non-responders. The high-dose responder demonstrated a 7αC4:sBA ratio of 12 times baseline prior to administration of 560 µg/kg/day of maralixibat, which increased to 1770 times baseline upon administration of the higher dose.

[00799] Not wishing to be limited by any particular mechanism of action, patients with greater retained canicular transport (as in the mild PFIC 2 patients) may require higher doses of maralixibat to block absorption of BA than those patients with lower retained canicular transport. Further, patients with biochemical effect (increase in 7αC4:sBA ratio) but not clinical response may be rescued with higher maralixibat doses.

[00800] A further surprising result was observed in the INDIGO clinical study. Low-dose responders demonstrated improved growth relative to baseline, whereas non-responders did not, see Fig. 4. Improved growth was measured using height Z-score and was defined as a positive height Z-score change relative to baseline height Z-scores measured prior to administration of maralixibat. Furthermore, the high dose responder also exhibited an increase in height Z-score following treatment response on sBA.

[00801] Twelve patients participated in a long-term extension of the INDIGO clinical study. Figures 5-8 plot measurements of cholestasis markers taken for all participants in the

INDIGO clinical study over time. The high-dose responder was first administered a daily dose of 560 μg/kg/day (2 equal doses of 280 μg/kg daily, BID) at between 547 and 638 days, see Fig. 5A. The high-dose responder demonstrated an increase in 7αC4:sBA ratio following administration of the higher dose, see Fig. 8. A low-dose responder demonstrating an increase in sBA concentration, a decrease in serum 7αC4 concentration, and a decrease in 7αC4:sBA ratio during the long-term extension was administered a higher dose of maralixibat (280 μg/kg BID) at between 640 and 730 days, see Figs. 5A and 6-8. Following the administration of the higher dose, sBA concentration decreased, severity of pruritus decreased, serum 7αC4 concentration increased, and 7αC4:sBA ratio increased, see Figs. 5A and 6-8. One low-dose responder demonstrated an increase in sBA during the long-term extension and was therefore administered a higher dose of maralixibat (280 μg/kg BID) at between 820 and 910 days, see Fig. 6. The severity of pruritus subsequently decreased, see Fig. 6, and the 7αC4:sBA ratio increased, see Fig. 8.

[00802] In the long-term extension of the INDIGO clinical study, no patients having an *ABCB11* gene with a truncating mutation were responders, see Fig. 5B.

[00803] One non-responder demonstrated an initial increase in 7αC4:sBA ratio before 90 days, which subsequently decreased, see Fig. 8. This non-responder may have demonstrated a response if the non-responder had been administered a higher dose of maralixibat (e.g., 280 μg/kg BID) prior to being withdrawing from the INDIGO clinical study. The initial increase, or spike, in 7αC4:sBA ratio indicates that this patient may have been capable of demonstrating a response (i.e., a clinical response) to maralixibat administration.

[00804] Responders in the INDIGO study maintained a response to maralixibat for over a year and for up to or beyond 5 years, see Figs. 5-8. Patients with non-truncating BSEP deficiency demonstrated durable control of pruritus and cholestasis with maralixibat, see Figs. 5-8. Figs. 5-8 demonstrate that 7αC4:sBA ratio is a good predictor of response to ASBTI.

[00805] Responders had genotypes consistent with residual BSEP function, whereas some non-responders had genotypes consistent with total lack of BSEP function.

Example 2. Dose-dependent fecal bile acid excretion with apical sodium-dependent bile acid transporter inhibitors maralixibat and volixibat in a dose-ranging phase 1 clinical study (NTC02475317) in overweight and obese adults

[00806] Multiple oral doses of maralixibat, volixibat, or placebo were administered once (QD) or twice (BID) for 7 days in overweight and obese adults on a low-fiber diet.

Participants had a body mass index of from 25 kg/m^2 to 35 kg/m^2. Participants consumed a low-fiber diet (< 10 mg/day) for 2 days before randomization and during the 7-day treatment period. Measurements were taken of fBA, sBA concentration, and serum 7αC4 concentration (which is a biomarker of bile acid synthesis) prior to drug administration and at day 7.

[00807] A summary of demographics and baseline fBA for participants to which each drug at each indicated dosage was administered is provided in Table 10. Overall demographics for all patients participating in the study are also provided in Table 10.

Table 10: Summary of demographics and baseline characteristics for participants in a phase 1, blinded, placebo-controlled, dose-ranging clinical study (NCT02475317). BID, twice daily; QD, once daily; SD, standard deviation; n, number of participants; multiple = mixed race (black and white).

	Placebo	Maralixibat						Volixibat		
		10 mg QD	20 mg QD	50 mg QD	100 mg QD	50 mg BID	All doses	10 mg QD	20 mg QD	All doses
n	14	10	10	10	10	10	50	10	10	20
Mean age, year (SD)	38.2 (9.32)	45.4 (11.18)	32.2 (8.92)	36.4 (12.87)	38.5 (9.87)	39.4 (12.66)	38.4 (11.58)	37.5 (6.74)	43.7 (14.40)	40.6 (11.39) 3
Race, n (%)										
White	7 (50.0)	6 (60.0)	3 (30.0)	7 (70.0)	7 (70.0)	6 (60.0)	29 (58.0)	6 (60.0)	515201	11 (55.0)
Black	6 (42.9)	4 (40.0)	7 (70.0)	3 (30.0)	3 (30 0)	4 (40.0)	21 (420)	4 (40.0)	4 (40.0)	8 (40.0)
Black & White	1 (7.1)	0	0	0	0	0	0	0	1 (10.0)	1 (5.0)
Mean fBA excretion, µmol (SD)	246.44 (113.597)	200.91 (176.918)	138.46 (91.660)	192.40 (235.828)	230.39 (231.489)	199.31 (147.859)		160.91 (129.561)	263.19 (287.653)	

[00808] Of 84 participants, 50 were randomized to maralixibat, 20 to volixibat, and 14 to placebo, see Table 10. All participants completed the study. Mean baseline fBA excretion ranged from 138 μmol to 240 μmol (SD, 92-231) across maralixibat doses and 161 μmol to 263 μmol (SD, 130-288) across volixibat doses and was 246 μM (SD, 114) for placebo, see Table 10.

[00809] fBA excretion increased in a dose-dependent manner for maralixibat and volixibat, with no notable change for placebo, see Fig. 9. Mean change from baseline was similar at the highest maralixibat doses: 1251 μmol (95% confidence interval, 539-1963) for 50 mg BID and 1144 μmol (95% confidence interval, 823-1466) for 100 mg QD, see Fig. 9. At the 10 mg dose for maralixibat and volixibat, mean change from baseline was 515 μmol (95% confidence interval, 196-835) and 744 μmol (95% confidence interval, 230-1257), respectively, see Fig. 9. At the 20 mg dose for maralixibat and volixibat, mean change from baseline was 532 μmol (95% confidence interval, 60-1005) and 874 μmol (95% confidence interval, 457-1290), respectively, see Fig. 9.

[00810] Mean serum 7αC4 increased with administration of maralixibat or volixibat, with the greatest change observed at a maralixibat dose of 50 mg BID, see Fig. 10.

[00811] No notable change in sBA or 7αC4 was observed with placebo, see Figs. 9-10. Mean baseline sBA levels were not elevated with administration of maralixibat or volixibat but did increase by 2.6 ng/mL (95% confidence interval, 1.2-3.9) with placebo. All treatment-emergent adverse events were mild, and none were serious. The proportion of participants with treatment-emergent adverse events did not differ among volixibat and maralixibat doses, or between maralixibat and volixibat. The only treatment-emergent adverse events occurring in over 10% of participants were headache and diarrhea.

[00812] Increases in fBA excretion were dose-dependent up to the maximum tested doses of volixibat and maralixibat, see Fig. 9. Safety outcomes were similar across tested dose ranges and between compounds.

[00813] At the highest daily doses of maralixibat, increases in fBA excretion were numerically higher with 50 mg BID than with 100 mg QD, see Fig. 9.

Example 3. Safety and efficacy of maralixibat in participants with primary sclerosing cholangitis (PSC): a 14-week, single-arm, open-label, phase 2a, proof-of-concept study of maralixibat (the CAMEO clinical trial; ClinicalTrials.gov: NTC02061540)

[00814] The CAMEO clinical trial included a 6-week dose-escalation period (maralixibat 0.5 mg/day, 1 mg/day, 2.5 mg/day, 5 mg/day, and 7.5 mg/day) followed by an 8-week dose-maintenance period (maralixibat 10 mg/day) and a 4-week follow-up period.

[00815] Participants were adults aged 18-80 years with a diagnosis of PSC. PSC diagnosis included a documented history of alkaline phosphatase (ALP) levels greater than 1.5 times above the upper limit of normal, biliary obstruction, and histological findings consistent with PSC diagnosis (if previously biopsied). The study enrolled 27 adults.

[00816] Efficacy was assessed by measuring at baseline and throughout the study sBA concentration, serum 7αC4 concentration (a marker of *de novo* bile acid synthesis), serum aoutotaxin concentration, LDL-C concentration, serum total cholesterol concentration, serum liver enzyme concentrations, and pruritus severity. Pruritus severity was determined by calculating Adult Itch Reported Outcome (ITCHRO) weekly sum scores and average daily scores (mean score over a 7-day period). Participants self-reported the ITCHRO daily on a scale 0-10 (0 = no pruritus; 10 = most severe pruritus).

[00817] Baseline mean serum alkaline phosphatase concentration for participants in the CAMEO study was 471.6 U/L (SD, 316.9).

[00818] Outcomes were assessed in the overall study population and in subgroups of participants (A) with any pruritus at baseline or (B) with an ITCHRO average daily score ≥4 out of 10 at baseline. Efficacy endpoints were based on change from baseline to week 14 or early termination (ET) and were analyzed using paired *t*-tests or Wilcoxon signed rank tests.

[00819] Of 27 enrolled participants, 23 (85.2%) completed the study. Participants were predominantly male (66.7%) and white (85.2%), with a mean age of 43.7 years (standard deviation [SD], 11.35) at study enrollment. Mean time since PSC diagnosis was 94 months (SD, 75.4). PSC symptoms of inflammatory bowel disease and ulcerative colitis were reported by 44.4% and 55.6% of participants, respectively.

[00820] ITCHRO weekly sum scores decreased from baseline by 51% (p=0.0495) overall, by 53% (p=0.0275) in participants with any pruritus at baseline (n=18), and by 70% (p=0.0313) in participants with an ITCHRO daily score ≥4 out of 10 at baseline (n=6), see Fig. 11. ITCHRO

average daily score improved by >3 points in 6 of 27 (22.2%) participants and improved by >1 point in 8 out of 27 (29.6%) participants. No participants experienced worsening of pruritus by >1 point from baseline to week 14. Pruritus improved in all 6 participants with an ITCHRO score ≥4 at baseline, see Table 11 and Fig. 11.

Table 11: ITCHRO scores for participants in the CAMEO clinical study with an ITCHRO daily score ≥4 at baseline

Participant	ItchRO average daily score (0-10 scale)		
	Baseline	**Week 14/ET**	**Change from baseline to week 14/ET**
A	9.1	0	-9.1
B	4.7	0	-4.7
C	5.9	1.3	-4.6
D	6.9	5.1	-1.7
E	6.9	3.1	-3.7
F	6.0	2.3	-3.7

ET, early termination; ItchRO, Itch Reported Outcome.

[00821] sBA levels decreased from baseline by 38% (mean -14.8 μmol/L [SD, 31.4]; p=0.0043) overall and by 45% in participants with an ITCHRO daily score ≥4 at baseline, see Fig. 12. Mean levels of 7αC4 increased from baseline by 130% (mean, 11.1 ng/mL [SD, 13.6]; p<0.0001) overall and by 107% in participants with an ITCHRO daily score ≥4 at baseline, see Fig. 12.

[00822] In the overall population of participants in the CAMEO clinical trial, significant reductions were observed in serum autotaxin concentration (-148 ng/mL [SD, 319]; p=0.0462) and serum LCL-C concentration (-16.3 mg/dL [SD, 17.6]; P<0.0001), see Fig. 13. In participants with an ITCHRO daily score ≥4 at baseline, significant reductions were observed in autotaxin levels, see Fig. 13. Reductions were observed in levels of total cholesterol in the overall population (mean change, -21.2 mg/dL [SE, 4.90; SD, 25.5]; p=0.0002) and in participants with an ITCHRO daily score ≥4 at baseline (mean change, -32.0 mg/dL [SE, 13.38]; p=0.06).

[00823] Mean conjugated bilirubin levels increased by 0.19 mg/dL (SE, 0.09, $p<0.0462$; SE, 0.450) in the overall population, with no significant change in participants with ITCHRO daily score ≥ 0 at baseline. Changes in serum total bilirubin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase concentrations were not statistically significant in participants in the CAMEO clinical study.

[00824] Statistically significant reductions in pruritus and sBA were observed after 14 weeks of treatment with maralixibat in the CAMEO clinical study, which is consistent with a proposed mechanism of action for maralixibat, see Fig. 1. Levels of serum autotaxin, a potential marker for cholestatic pruritus, also improved in a statistically significant manner, see Fig. 13. Mean percent reductions were greater in pruritus and sBA and autotaxin levels in participants with an ITCHRO daily score ≥ 4 at baseline than in the overall participant population for the CAMEO study, see Fig. 14.

[00825] Statistically significant reductions in serum LDL-C levels and statistically significant increases in serum 7αC4 levels indicated *de novo* synthesis of bile acids from cholesterol, which is consistent with ASBT inhibition.

[00826] Maralixibat was well tolerated in the CAMEO study and associated with reduced serum BA levels in adults with PSC. In addition, autotaxin levels reduced and pruritus improved significantly from BL, with the greatest reductions in those with worst pruritus at baseline.

Example 4. Durability of treatment effect with long-term maralixibat in children with Alagille syndrome: 4-year efficacy results from a Phase 2b double-blind, randomized, placebo-controlled drug-withdrawal study with a long-term open-label pretreatment period of maralixibat 400 µg/kg/day twice daily (BID) (the ICONIC clinical study)

[00827] Children aged 1-18 years with a diagnosis of ALGS and evidence of cholestasis were eligible to enroll in the ICONIC clinical study, see Tables 12-14. During a long-term extension, participants with sBA levels above the upper limit of normal and/or an ITCHRO(OBS) score > 1.5 were eligible for the 400 µg/kg BID dose (all participants received the 400 µg/kg BID dose). Inclusion criteria for the ICONIC study included having cholestasis, which was defined as at least one of 1) sBA concentration (total sBA) >3x the upper limit of normal, 2) serum conjugated bilirubin concentration >1 mg/dL, 3) fat-soluble vitamin deficiency not otherwise explained, 4) serum gamma-glutamyl transferase concentration >3x the upper limit of normal, and 3) intractable pruritus explainable only by liver disease. Inclusion criteria also included having

significant pruritus, which was defined as an average daily score of >2 on the ITCHRO(OBS) scale for 2 consecutive weeks (0 = no pruritus; 4 = most severe pruritus). Exclusion criteria included having surgically disrupted enterohepatic circulation, a liver transplant, decompensated cirrhosis, or having any liver disease other than ALGS.

Table 12: Disposition and demographics for participants in the ICONIC clinical study.

Disposition and demographics	
Median Age (range), years	5.4 (1-15)
Male, %	61.3
Genotype, n (%)	
JAG1	31 (100)
Enrolled, n	31
Randomized week 18, n	29
Maralixibat	13
Placebo	16
Completed week 48, n	28

Table 13: Baseline characteristics for participants in the ICONIC clinical study. ALT, alanine transaminase.

Baseline characteristics, mean (SD)	
ItchRO (Obs), 0-4	2.9 (0.5)
CSS, 0-4	3.3 (0.9)
sBA, μmol/L	283 (211)
C4, ng/mL	10.3 (14.7)
Total bilirubin, mg/dL	6.1 (5.8)
Direct bilirubin, mg/dL	4.6 (3.7)
ALT, U/L	181 (109)
Clinician xanthoma scale, 0-4	0.9 (1.26)
PedsQL, 0-100	61.2 (17.3)

[00828] sBA responders were defined as those patients achieving ≥ 50% reduction from baseline in sBA at week 12 or 18. ITCHRO responders were defined as those patients achieving at least a 1-point reduction from Baseline in weekly morning ITCHRO(OBS) score at week 12 or 18.

[00829] A summary of the experimental design for the ICONIC clinical study is provided as Fig. 15. After completion of the 48-week core study at a dose of 400 μg/kg daily (QD), participants were able to continue long-term treatment with maralixibat 400 μg/kg QD (the

extension portion of the study). In the open label extension, the effect of higher doses was explored by increasing dosage to a maximum of 400 μg/kg BID in eligible participants.

[00830] Efficacy assessments were based on changes from baseline in sBA concentration, weekly average ITCHRO(OBS) scores (0, none; 4, most severe), CSS score (0, none; 4 most severe), and Clinician Xanthoma Scale score (0, none; 4, disabling). During a randomized withdrawal period (week 18-22), differences between maralixibat and placebo in sBA concentration and ITCHRO(OBS) scores were evaluated. During the long-term extension, efficacy assessments were conducted every 12 weeks. Serum total cholesterol and serum 7αC4 concentration were also monitored during the ICONIC clinical study, among other measures.

[00831] sBA were measured using a fully validated liquid chromatography-electrospray ionization-mass electrospray (LC-ESI-MS) method using stable-isotope dilution analysis to measure serum concentrations of principal bile acids (cholic, chenodeoxycholic, ursodeoxycholic, deoxycholic acid, lithocholic, and their corresponding glycine and taurine conjugates). Serum samples were analyzed in the Division of Pathology and Laboratory Medicine, Cincinnati Children's Hospital Medical Center according to SOP # PATH.CMS.1033. Calibration standards of individual bile acids were in the range of 50-25,000 ng/mL and Quality Control samples were prepared at concentrations of 100, 500, 1000, 2500, and 20000 ng/mL. The intra- and inter-assay imprecision of the method for individual bile acids measured was within the accepted GLP quality assurance guidelines of < 15% coefficient of variance for these QC samples. The lower limit of quantification of the assay was set at 100 ng/mL and the imprecision at this concentration was <20%. The limit of detection of the assay was 5 ng/mL. Total sBA is represented by the sum of the individual bile acid species measured.

[00832] Of the 28 participants who completed the core study (up to week 48), 23 consented to long-term extension. After 2 years, 15 participants continued in the extension phase with a dose increase to 400 μg/kg BID, see Figs. 15-16. Table 14 provides baseline characteristics and demographics for participants in the long-term extension.

Table 14: Baseline characteristics and demographics for participants enrolled in the ICONIC clinical study and participants in the long-term extension of the ICONIC clinical study

	Enrolled participants (N = 31)	**Extension participants (N = 15)**
Median age (range), years	5.0 (1–15)	5.0 (1-12)
Male, n (%)	19 (61.3)	10 (66.7)
JAG1 mutation , n (%)	31 (100.0)	15 (100.0)
Serum bile acid level, µmol/L	283.4 (37.8)	259.0 (55.3)
Total Bilirubin mg/dL	6.1 (1.0)	3.2 (0.9)
ItchRO(Obs) score (0-4)	2.9 (0.1)	2.8 (0.1)
CSS score (0-4)	3.3 (0.2)	3.2 (0.3)
Height z-score	–1.7 (0.2)	-1.8 (0.3)

Data presented as mean (SE) unless otherwise specified.

[00833] sBA concentration decreased by 31% (p = 0.0005) during the first 18 weeks of treatment with maralixibat at 400 µg/kg QD, see Figs. 17-18 and 32. During randomized withdrawal, sBA levels returned to baseline in the placebo group but were maintained in the maralixibat groups (least squares [LS] mean difference, -114.0; SE, 48.0; p = 0.03), see Figs. 17-18 and 32. Reductions in sBA levels were maintained and continued to improve during the long-term extension, see Figs. 18 and 19. At 191 weeks, sBA levels were reduced by about 57% from baseline (p = 0.0047), see Fig. 19.

[00834] Serum total cholesterol concentration and serum 7αC4 concentration both showed a statistically significant decrease from baseline by week 48 and week 191, see Table 15. A statistically significant decrease observed in serum total cholesterol concentration and serum 7αC4 concentration observed by week 49 was maintained through week 191 of the ICONIC clinical study, see Table 15.

Table 15: Serum cholesterol concentration (mg/dL) and serum 7αC4 concentration (ng/mL) at baseline, week 48, and week 191 and a comparison of the week 49 and week 191 measurements to the baseline measurements for participants in the ICONIC clinical study.

Mean (SD)	**Baseline n = 15**	**Week 48 n = 15**	**Week 191 n = 15**
Serum cholesterol, mg/dL	414.3 (182.1)	340.3 (149.9)	277.5 (65.7)
p value[a]		< 0.01	< 0.01
C4, ng/mL	7.4 (8.7)	20.4 (32.2)	30.4 (44.6)
p value[a]		0.1	0.04

[00835] ITCHRO(OBS) scores decreased from baseline (mean change, -1.7; SE, 0.2; $p < 0.0001$) during the first 18 weeks of treatment with maralixibat at 400 µg/kg QD, see Figs. 20, 23 and 32. During randomized withdrawal, pruritus worsened in the placebo group but not in the maralixibat group (LS mean difference, -1.5; SE, 0.3, $p = 0.0001$), see Figs. 20, 21, 23, 25 and 32 and Table 16. At 191 weeks, ITCHRO(OBS) score was reduced from baseline (mean change, -2.5; SE, 0.2; $p < 0.0001$), see Figs. 22-23. Improvement in pruritus was also demonstrated by a mean reduction in CSS score at 191 weeks of 2.4 points (SE, 0.4; $p < 0.0001$), Fig. 22, and a mean reduction in ITCHRO(OBS) score at 193 weeks of over 2 points to a final score of about 0.33 (SE, 0.2; $p < 0.0001$), see Figs. 23 and 24. Also, CSS scores decreased by over 1.5 points (final average score of about 1.5) on average by week 48 across all participants, Fig. 22, and ITCHRO(OBS) scores decreased by over 1.5 points on average (final average score of about 0.33) relative to baseline by week 193, see Figs. 23 and 24. Control of pruritus improved over time, with over 89% of study days across participants reported by observers as minimal or no pruritus (ITCHRO(OBS) ≤ 1) after 98 weeks, see Figs. 21-25.

Table 16: A greater proportion of ITCHRO(OBS) responders were observed in a maralixibat group than placebo during withdrawal in the ICONIC clinical study

ItchRO (Obs) responder criteria	Open-label Week 18	Withdrawal – Week 22		Open-label Week 48
		Maralixibat	Placebo	
Decrease from baseline ≥1	67.7%	53.8% (p = 0.14)	25.0%	72.4%
Decrease from baseline ≥1.25	58.1%	46.2% (p = 0.09)[a]	12.5%	58.6%
Decrease from baseline ≥1.5	51.6%	23.1% (p = 0.01)[a]	0%	51.7%

[00836] Reductions in sBA concentration and pruritus severity continued and were further improved during the extension, see Figs. 18-19 and 22-24, and xanthomas continued to be re-absorbed ($p<0.05$), see Fig. 29. CSS scores continued to improve during the extension ($p<0.0001$). Improvements were seen in PedsQL Multidimensional Fatigue Scale scores ($p<0.01$) during the ICONIC core study and extension, see Figs. 26-27. Therefore, maralixibat improved quality of life.

[00837] Clinician Xanthoma Score was reduced by 0.7 points (SE, 0.3; $p = 0.0285$) from baseline in participants in the ICONIC clinical study by week 191. Clinician xanthoma scale scores improved significantly ($p < 0.01$) across all participants by week 48, see Fig. 28. Xanthomas continued to be reabsorbed during the long-term extension, see Fig. 29. Thus, maralixibat improved xanthomas.

[00838] Maralixibat was well tolerated during the core study and extension of the ICONIC clinical study for a period of over three years. Treatment effect was maintained over a period exceeding 48 weeks. Serum concentrations of GGT, ALT, AST, and bilirubin were monitored throughout the ICONIC clinical study, see Fig. 30.

[00839] Therapeutic benefits of maralixibat in children with ALGS were clinically relevant and statistically significant. Continuation of maralixibat treatment following a withdrawal period maintained significantly lower sBA levels and less severe pruritus than placebo during the randomized placebo-controlled drug-withdrawal period. Maralixibat significantly reduced pruritus and sBA levels over time and versus placebo in children with ALGS. Long-term maralixibat treatment was associated with durable control of sBA levels, pruritus, and

xanthomas, as well as improved growth (discussed further below). Maralixibat was generally well tolerated at doses up to 800 µg/kg/day and with treatment duration up to 4 years.

[00840] A positive correlation was observed between reduction in sBA concentration and reduction of severity of pruritus as measured by the ITCHRO(OBS) scale, see Figs. 31-32 and Tables 17-19.

Table 17: ITCHRO(OBS) weekly morning average score by sBA response definition for participants in the ICONIC clinical study. A reduction in sBA concentration showed a positive correlation with a reduction in ITCHRO(OBS) weekly morning average score, as compared to baseline.

		ItchRO(Obs) Weekly Morning Average Score	
sBA Response Definition	Week 48 (N=28) n (%)	Week 48 Average Score	Average Change from Baseline
≥50% Reduction	13 (46.4%)	1.07	-1.86
≥60% Reduction	11 (39.3%)	0.82	-2.12
≥70% Reduction	8 (28.6%)	0.62	-2.31
≥80% Reduction	4 (14.3%)	0.11	-2.79
≥90% Reduction	1 (3.6%)	0.00	-2.71
Normalization (<8.5 µmol/L)	1 (3.6%)	0.00	-3.50

Table 18: sBA concentrations and change in ITCHRO(OBS) weekly morning average score from baseline for participants (subjects) in the ICONIC clinical study at week 48.

	Serum Bile Acid (µmol/L)			Change in ItchRO from Baseline to Week 48
Subject ID	Baseline	Week 48	Change from Baseline to Week 48	
001021	79.4	22.9	-56.4	-0.12
001022	298.1	131.8	-166.3	0.49
001023	379.9	98.5	-281.4	-0.45
040001	411.8	578.1	166.4	1.29
040002[a]	503.2			
040003	142.0	20.8	-121.1	-3.86
050001	328.7	333.0	4.3	0.00

050003	370.5	119.6	-251.0	-2.57
050004	114.5	117.7	3.3	-1.86
050005	519.9	492.6	-27.3	-1.71
050006	583.4	427.9	-155.5	-1.00
050007	440.0	199.8	-240.2	-1.29
051001	20.2	29.2	9.0	-1.67
051002	748.5	891.6	143.1	-1.14
052002	275.6	163.4	-112.2	-1.71
060001	43.8	60.2	16.4	-1.03
060002	22.8	12.0	-10.9	-3.29
060003	40.5	23.6	-16.9	-3.43
060004	71.6	126.1	54.5	-2.50
061001	657.4	37.0	-620.4	-2.71
061002	30.9	7.0	-23.9	-3.50
061004	479.2	101.9	-377.3	-3.29
061005	499.2	293.3	-205.9	-1.00
061006	335.4	65.0	-270.4	-2.71
080001	85.4	110.9	25.5	-2.29
80003	239.4	35.8	-203.6	-1.86
090001	203.7	208.0	4.3	-0.17
090002	152.2	55.8	-96.4	-1.43
090003	49.5	15.6	-33.9	-0.83
090004[a]	496.9			
090005[a]	162.8			

[a]Subjects do not have data beyond baseline due to early discontinuations prior to Week 48.

Table 19: ITCHRO(OBS) morning average score and sBA reduction levels for participants (subjects) in the ICONIC clinical study.

	ItchRO(Obs) Weekly Morning Average Score			Serum Bile Acid	
Subject ID	Baseline	Week 48	Change from Baseline to Week 48	Normalization at Week 48 (< 8.5 µmol/L) (Y or N)	Reduction of ≥ 80% from Baseline to Week 48 (Y or N)
001021	2.83	2.71	-0.12	N	N
001022	2.71	3.20	0.49	N	N
001023	2.29	1.83	-0.45	N	N
040001	2.43	3.71	1.29	N	N

040002[a]	3.14				
040003	4.00	0.14	-3.86	N	Y
050001	1.86	1.86	0.00	N	N
050003	3.29	0.71	-2.57	N	N
050004	3.00	1.14	-1.86	N	N
050005	2.00	0.29	-1.71	N	N
050006	3.00	2.00	-1.00	N	N
050007	3.00	1.71	-1.29	N	N
051001	2.67	1.00	-1.67	N	N
051002	3.14	2.00	-1.14	N	N
052002	3.43	1.71	-1.71	N	N
060001	2.43	1.40	-1.03	N	N
060002	3.29	0.00	-3.29	N	N
060003	3.43	0.00	-3.43	N	N
060004	2.50	0.00	-2.50	N	N
061001	2.71	0.00	-2.71	N	Y
061002	3.50	0.00	-3.50	Y	N
061004	3.29	0.00	-3.29	N	N
061005	2.43	1.43	-1.00	N	N
061006	2.71	0.00	-2.71	N	Y
080001	3.86	1.57	-2.29	N	N
080003	2.14	0.29	-1.86	N	Y
090001	3.67	3.50	-0.17	N	N
090002	2.57	1.14	-1.43	N	N
090003	3.00	2.17	-0.83	N	N
090004[a]	3.57				
090005[a]	2.29				

[a]Subjects do not have data beyond baseline due to early discontinuations prior to Week 48.

[00841] Height Z-score increased by 0.5 (SE, 0.1; p = 0.0027) from baseline in participants in the ICONIC clinical study, see Figs. 33-34. This corresponds to a statistically significant acceleration in height growth. Therefore, maralixibat improved growth relative to baseline in patients suffering ALGS. Moreover, a further increase in growth from baseline was observed when patients (N = 15) were administered 400 µg/kg BID of maralixibat after having been administered a 400 µg/kg QD of maralixibat for a period in excess of about 40 weeks. Also, further improvements in sBA, pruritus, and growth were observed following administration of the higher daily dose relative to improvements observed with administration of 400 µg/kg QD of

maralixibat, see Figs. 18 and 23. The increase in growth was also observed as an increase in weight Z-scores, see Figs. 35-36. As with the height Z-score, administration of maralixibat caused a dose-dependent increase in weight Z-scores, see Figs. 35-36. Participants administered maralixibat at a dose of 400 µg/kg BID of maralixibat after having been administered a 400 µg/kg QD of maralixibat for a period in excess of about 40 weeks demonstrated a greater increase in weight Z-score at 400 µg/kg BID than at 400 µg/kg QD.

[00842] All references cited anywhere within this specification are incorporated herein by reference in their entirety for all purposes.

[00843] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only.

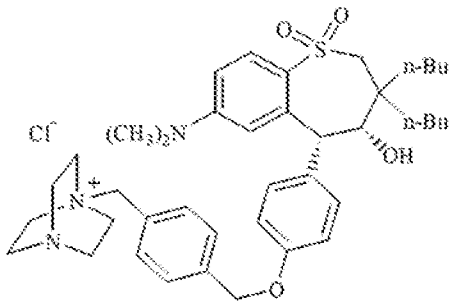
[00844] Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range and each endpoint, unless otherwise indicated herein, and each separate value and endpoint is incorporated into the specification as if it were individually recited herein.

[00845] Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

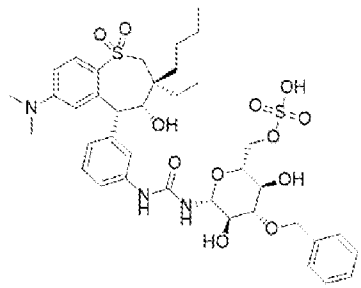
Claims

1. A method for treating or ameliorating cholestatic liver disease in a subject in need thereof, wherein the subject has a bile salt export pump (BSEP) deficiency, the method comprising administering to the subject an Apical Sodium-dependent Bile Acid Transport Inhibitor (ASBTI).

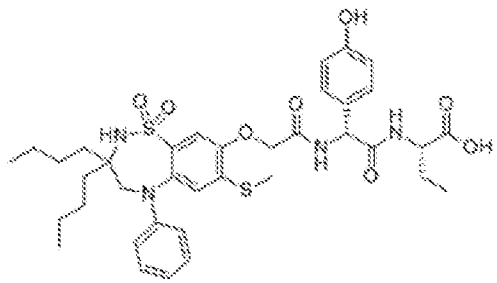
2. The method of claim 1, wherein the ASBTI is



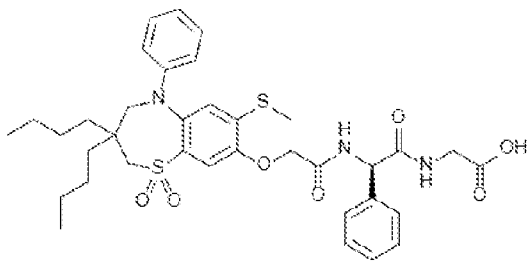
(maralixibat),



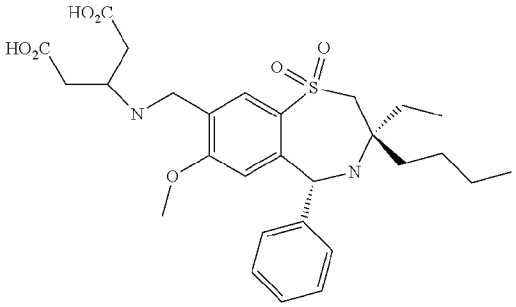
(volixibat),



(odevixibat),



(elobixibat),



(GSK2330672), or a pharmaceutically acceptable salt thereof.

3. The method of claim 2, wherein the ASBTI is maralixibat, or an alternative pharmaceutically acceptable salt thereof.

4. The method of claim 2, wherein the ASBTI is volixibat, or a pharmaceutically acceptable salt thereof.

5. The method of claim 2, wherein the ASBTI is odevixibat, or a pharmaceutically acceptable salt thereof.

6. The method of claim 2, wherein the ASBTI is elobixibat, or a pharmaceutically acceptable salt thereof.

7. The method of claim 2, wherein the ASBTI is GSK2330672, or a pharmaceutically acceptable salt thereof.

8. The method of any one of claims 1-7, wherein the cholestatic liver disease is progressive familial intrahepatic cholestasis type 2 (PFIC 2), benign recurrent intrahepatic cholestasis (BRIC) or intrahepatic cholestasis of pregnancy (ICP), or biliary atresia.

9. The method of any of claims 1-8, wherein the subject has residual BSEP function.

10. The method of claims 1-9, wherein the BSEP deficiency results in impaired or reduced bile flow or cholestasis.

11. The method of any of claims 1-10, wherein an *ABCB11* gene of the subject comprises a non-truncating mutation.

12. The method of claim 11, wherein the *ABCB11* gene comprises one or more of E297G, D482G, an alternative missense mutation, or a combination thereof.

13. The method of claim 11, wherein the *ABCB11* gene comprises an E297G or a D482G mutation, or both.

14. The method of any of claims 11 or 12, wherein the *ABCB11* gene comprises a missense mutation and not an E297G or D482G mutation.

15. The method of any of claims 1-13 further comprising determining a genotype of the subject.

16. The method of claim 15, wherein determining the genotype comprises identifying and characterizing a mutation in the *ABCB11* gene.

17. The method of claim 16 wherein the *ABCB11* gene of the subject is characterized as comprising only non-truncating mutations.

18. The method of claim 1 comprising determining a ratio of serum 7α-hydroxy-4-cholesten-2-one (7αC4) concentration to serum bile acid (sBA) concentration (7αC4:sBA) prior to administering the ASBTI at a first dose level (baseline ratio), and further determining 7αC4:sBA after the ASBTI administration, wherein the ASBTI administration results in a 7αC4:sBA ratio about 2-fold or greater higher than the baseline 7αC4:sBA ratio.

19. The method of claim 18, wherein if the 7αC4:sBA ratio begins to decrease or decreases to less than 2-fold or greater higher than baseline, a second dose level of the ASBTI is administered to the subject, wherein the second dose level is higher than the first dose level.

20. The method of claim 1, comprising determining a ratio of serum 7αC4 concentration to sBA concentration (7αC4:sBA) prior to administering the ASBTI at a first dose level

(baseline ratio), and further determining 7αC4:sBA after the ASBTI administration, wherein if the ASBTI administration fails to result in a 7αC4:sBA ratio about 2-fold or greater higher than the baseline 7αC4:sBA ratio, the subject is administered a second dose level of the ASBTI, wherein the second dose level is higher than the first dose level.

21. The method of claim 1, further comprising modulating a dose of the ASBTI, the modulating comprising determining a ratio of serum 7αC4 concentration to sBA concentration (7αC4:sBA) prior to administering the ASBTI at a first dose level (baseline ratio), and further determining 7αC4:sBA after the ASBTI administration, wherein if the ASBTI administration fails to result in a 7αC4:sBA ratio about 2-fold or greater higher than the baseline 7αC4:sBA ratio the ASBTI is then administered at a second dose level that does result in a 7αC4:sBA ratio that is about a 2-fold or greater higher than the baseline ratio.

22. The method of claim 1, further comprising modulating a dose of the ASBTI, the modulating comprising determining a ratio of serum 7αC4 concentration to sBA concentration (7αC4:sBA) prior to administering the ASBTI at a first dose level (baseline ratio), and further determining 7αC4:sBA after the ASBTI administration, wherein if a treating physician believes the ratio could be elevated beyond the current level with a higher dose level of the ASBTI, then the subject is administered the ASBTI at a second dose level that results in a 7αC4:sBA ratio that is higher than the baseline ratio.

23. The method of any of claims 19-22, wherein the second dose is at least about twice and less than about five times the first dose.

24. The method of any of claims 1-23, wherein the subject is a pediatric subject under 18 years of age.

25. The method of claim 24, wherein the administration of the ASBTI results in improved growth of the subject relative to baseline growth.

26. The method of claim 25, wherein the improved growth of the subject is measured as an increase in height z-score.

27. The method of any of claims 1-26, wherein the ASBTI is administered at a daily dose of from about 140 μg/kg to about 1400 μg/kg.

28. The method of claim 27, wherein the ASBTI is administered once daily.

29. The method of claim 27, wherein the ASBTI is administered twice daily.

30. The method of any of claims 1-29, wherein the ASBTI is administered at a daily dose of from about 5 mg/day to about 100 mg/day.

31. The method of any of claims 1-30, wherein the ASBTI is administered regularly for a period of at least one year.

32. The method of any of claims 1-31, wherein the ASBTI is administered regularly for a period of at least 4 years.

33. The method of any of claims 1-32, wherein the administration of the ASBTI results in a reduction in a symptom or a change in a disease-relevant laboratory measure of the cholestatic liver disease that is maintained for at least one year.

34. The method of claim 33, wherein the reduction in a symptom or a change in a disease-relevant laboratory measure comprises a reduction in sBA concentration, an increase in serum 7αC4 concentration, an increase in a ratio of serum 7αC4 concentration to sBA concentration (7αC4:sBA), a reduction in pruritis, an increase in a quality of life inventory score, an increase in a quality of life inventory score related to fatigue, or a combination thereof.

35. The method of claim 34, wherein the reduction in the symptom or a change in a disease-relevant laboratory measure is determined relative to a baseline level.

36. The method of any of claims 33 or 34, wherein the subject is a pediatric subject under 18 years of age, and the reduction in a symptom or a change in a disease-relevant laboratory measure comprises an increase in growth.

37. The method of any of claims 1-36, wherein the administration of the ASBTI results in an increase in serum 7αC4 concentration.

38. The method of claim 37, wherein the serum 7αC4 concentration is increased from about 1.5-fold to about 40-fold relative to baseline.

39. The method of any of claims 1-38, wherein the administration of the ASBTI results in an increase in a ratio of serum 7αC4 concentration to sBA concentration (7αC4:sBA).

40. The method of claim 39, wherein the 7αC4:sBA is increased by from about 2-fold to about 5,000-fold relative to baseline.

41. The method of any of claims 1-40, wherein the administration of the ASBTI results in an increase in fecal bile acids (fBA) of at least 100% relative to baseline.

42. The method of any of claims 1-41, wherein the administration of the ASBTI results in a decrease in sBA concentration of at least about 70% relative to baseline.

43. The method of any of claims 1-42, wherein the administration of the ASBTI results in a reduction in severity of pruritus.

44. The method of claim 43, wherein the reduction in severity of pruritis is measured as a reduction of at least 1.0 in an observer-reported itch reported outcome (ITCHRO(OBS)) score.

45. The method of claim 44, wherein the administration of the ASBTI results in an ITCHRO(OBS) score of ≤1.

46. The method of any of claims 1-45, wherein the administration of the ASBTI results in an increase in a quality of life inventory score.

47. The method of claim 46, wherein the quality of life inventory score is a health-related quality of life (HRQoL) score.

48. The method of claims 46 or 47, wherein the quality of life inventory score is a Pediatric Quality of Life Inventory (PedsQL) score, and wherein the PedsQL score is increased by at least 10% relative to baseline.

49. The method of any of claims 1-48, wherein the serum bilirubin concentration is at pre-administration baseline level at about 4 months after first administration of the ASBTI.

50. The method of any of claims 1-49, serum alanine aminotransferase (ALT) concentration is at pre-administration baseline level at about 4 months after first administration of the ASBTI.

51. The method of any of claims 1-50, wherein serum aspartate aminotransferase (AST) concentration, and serum bilirubin concentration are within a normal range at about 4 months after first administration of the ASBTI.

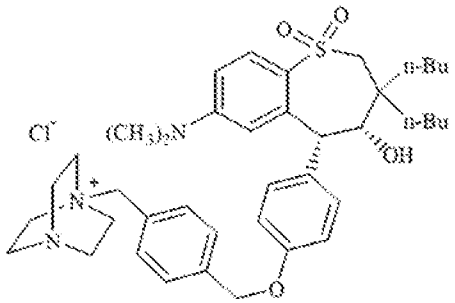
52. The method of any of claims 1-51, wherein the administration of the ASBTI results in serum ALT concentration decreasing by at least about 10% relative to baseline.

53. The method of any of claims 1-52, wherein the subject has biliary atresia or intrahepatic cholestasis of pregnancy.

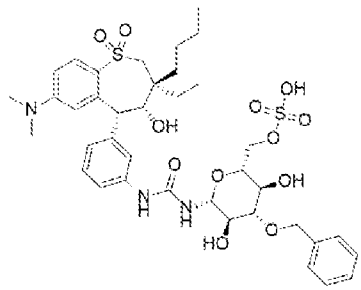
54. A method for predicting subject response to treatment of a cholestatic liver disease, wherein the treatment comprises administering to the subject in need of such treatment an

ASBTI, the method comprising determining a genotype of the subject, and predicting subject response to the treatment based upon the genotype.

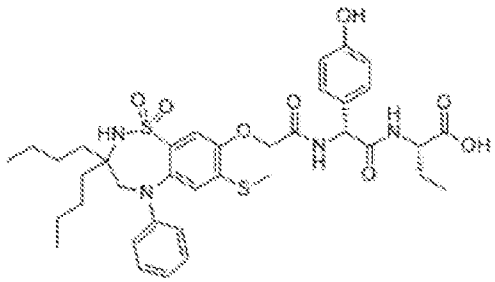
55. The method of claim 54, wherein the ASBTI is



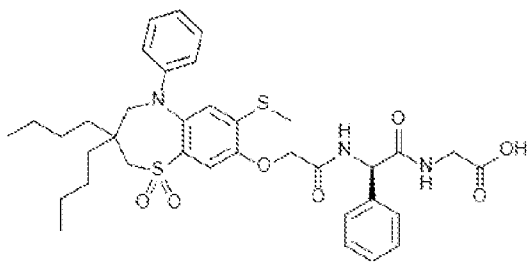
(maralixibat),



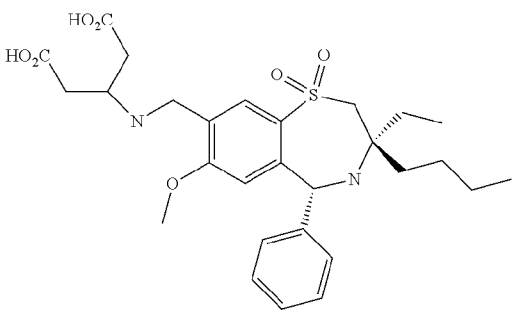
(volixibat),



(odevixibat),



(elobixibat),



(GSK2330672), or a pharmaceutically acceptable salt thereof.

56. The method of claim 55, wherein the ASBTI is maralixibat, or an alternative pharmaceutically acceptable salt thereof.

57. The method of claim 55, wherein the ASBTI is volixibat, or a pharmaceutically acceptable salt thereof.

58. The method of claim 55, wherein the ASBTI is odevixibat, or a pharmaceutically acceptable salt thereof.

59. The method of claim 55, wherein the ASBTI is elobixibat, or a pharmaceutically acceptable salt thereof.

60. The method of claim 55, wherein the ASBTI is GSK2330672, or a pharmaceutically acceptable salt thereof.

61. The method of any of claims 54-60, wherein determining the genotype comprises determining a sequence of an *ABCB11* gene.

62. The method of claim 61 further comprising identifying and characterizing a mutation of the *ABCB11* gene.

63. The method of claim 62 further comprising predicting that the subject will not be responsive to administration of the ASBTI if the *ABCB11* gene comprises a truncating mutation.

64. The method of any of claims 62 or 63 further comprising predicting that the subject will not be responsive to administration of the ASBTI if the *ABCB11* gene comprises a mutation resulting in total loss of BSEP activity.

65. The method of any of claims 54-64 further comprising predicting that the subject will be responsive to administration of the ASBTI if the *ABCB11* gene comprises mutations that

result in residual BSEP activity and the *ABCB11* gene comprises no mutations that result in absence of BSEP activity.

66. The method of claim 65, wherein the *ABCB11* gene comprises one or more of an E297G, D482G, an alternative missense mutation, or some combination thereof.

67. The method of any of claims 54-**Error! Reference source not found.**, further comprising administering an ASBTI to the subject if the subject is predicted to be responsive to the administration of the ASBTI.

68. The method of any of claims 54-67, wherein the subject has biliary atresia or intrahepatic cholestasis of pregnancy.

69. A method for treating or ameliorating cholestatic liver disease in a subject in need thereof, wherein the subject has a BSEP deficiency, the method comprising:

determining a genotype of the subject;

using the genotype of the subject to predict whether the subject will be or will not be responsive to treatment with an ASBTI; and

administering an ASBTI to the subject if the subject is predicted to be responsive to administration of the ASBTI.

70. The method of claim 69, wherein determining the genotype comprises determining a sequence of an *ABCB11* gene.

71. The method of claim 70 further comprising identifying and characterizing a mutation of the *ABCB11* gene.

72. The method of claim 71 further comprising predicting that the subject will not be responsive to administration of the ASBTI if the *ABCB11* gene comprises a truncating mutation.

73. The method of claim 71 further comprising predicting that the subject will not be responsive to administration of the ASBTI if the *ABCB11* gene comprises a mutation resulting in total loss of BSEP activity.

74. The method of claim 71 further comprising predicting that the subject will be responsive to administration of the ASBTI if the *ABCB11* gene comprises mutations that result in residual BSEP activity and the *ABCB11* gene comprises no mutations that result in absence of BSEP activity.

75. The method of any of claims 71 or 74, wherein the *ABCB11* gene comprises one or more of an E297G, D482G, an alternative missense mutation, or some combination thereof.

76. The method of claim 69 further comprising determining a ratio of serum 7αC4 concentration to serum bile acid (sBA) concentration (7αC4:sBA) prior to administering the ASBTI at a first dose (baseline ratio), and further determining the 7αC4:sBA after the ASBTI administration.

77. The method of claim 76, further comprising administering a second dose of the ASBTI, wherein the second dose is greater than the first dose, if after the administration of the first dose of the ASBTI the 7αC4:sBA is not maintained about >2-fold higher than the baseline ratio.

78. The method of claim 76, further comprising administering a second dose of the ASBTI, wherein the second dose is greater than the first dose, if the 7αC4:sBA initially increases by at least >2-fold higher than the baseline ratio and then begins to decrease back to the baseline ratio.

79. The method of any of claims 77 or 78, wherein the second dose is at least about twice and less than about five times the second dose.

80. The method of any of claims 69-79, wherein the subject is a pediatric subject under 18 years of age.

81. The method of claim 80, wherein the administration of the ASBTI results in improved growth of the subject.

82. The method of claim 81, wherein improved growth of the subject is measured as an increase in height z-score.

83. The method of any of claims 69-82, wherein the ASBTI is administered at a daily dose of from about 140 μg/kg to about 1400 μg/kg.

84. The method of any of claims 69-83, wherein the ASBTI is administered once daily.

85. The method of any of claims 69-84, wherein the ASBTI is administered twice daily.

86. The method of any of claims 69-85, wherein the ASBTI is administered at a dose of from about 5 mg/day to about 100 mg/day.

87. The method of any of claims 69-86, wherein the ASBTI is administered regularly for a period of at least one year.

88. The method of any of claims 69-87, wherein the ASBTI is administered regularly for a period of at least 4 years.

89. The method of any of claims 69-88 wherein the administration of the ASBTI results in a reduction in a symptom or a change in a disease-relevant laboratory measure of the cholestatic liver disease that is maintained for at least one year.

90. The method of claim 89, wherein the reduction in a symptom or a change in a disease-relevant laboratory measure comprises a reduction in sBA concentration, an increase in serum 7αC4 concentration, an increase in a ratio of serum 7αC4 concentration to sBA concentration (7αC4:sBA), a reduction in pruritis, an increase in a quality of life

inventory score, an increase in a quality of life inventory score related to fatigue, or a combination thereof.

91. The method of claim 90, wherein the reduction in the symptom or a change in a disease-relevant laboratory measure is determined relative to a baseline level.

92. The method of any of claims 89 or 90, wherein the subject is a pediatric subject under 18 years of age and the reduction in a symptom or a change in a disease-relevant laboratory measure comprises an increase in growth.

93. The method of any of claims 69-92, wherein the administration of the ASBTI results in an increase in serum 7αC4 concentration.

94. The method of claim 93, wherein the serum 7αC4 concentration is increased from about 1.5-fold to about 40-fold relative to baseline.

95. The method of claim 93, wherein the serum 7αC4 concentration is increased by at least 100% relative to baseline.

96. The method of any of claims 69-95, wherein the administration of the ASBTI results in an increase in a ratio of serum 7αC4 concentration to sBA concentration (7αC4:sBA).

97. The method of claim 96, wherein 7αC4:sBA is increased by from about 2-fold to about 5,000-fold relative to baseline.

98. The method of any of claims 69-97, wherein the administration of the ASBTI results in an increase in fBA of at least 100% relative to baseline.

99. The method of claim any of claims 69-98, wherein the administration of the ASBTI results in a decrease in sBA concentration of at least about 70% relative to baseline.

100. The method of any of claims 69-99, wherein the administration of the ASBTI results in a reduction in severity of pruritus.

101. The method of claim 100, wherein the reduction in severity of pruritis is measured as a reduction of at least 1.0 in an observer-reported itch reported outcome (ITCHRO(OBS)) score relative to baseline.

102. The method of claims 100 or 101, wherein the administration of the ASBTI results in an ITCHRO(OBS) score of ≤ 1.

103. The method of any of claims 69-102, wherein the administration of the ASBTI results in an increase in a quality of life inventory score.

104. The method of claim 103, wherein the quality of life inventory score is a health-related quality of life (HRQoL) score.

105. The method of any of claims 103 or 104, wherein the quality of life inventory score is a Pediatric Quality of Life Inventory (PedsQL) score.

106. The method of claim 105, wherein the PedsQL score is increased by at least 10% relative to baseline.

107. The method of any of claims 69-106, wherein serum bilirubin concentration is at pre-administration baseline level at about 4 months after first administration of the ASBTI.

108. The method of any of claims 69-107, wherein serum ALT concentration is at pre-administration baseline level at about 4 months after first administration of the ASBTI.

109. The method of any of claims 69-108, wherein serum ALT concentration, serum AST concentration, and serum bilirubin concentration being are within a normal range at about 4 months after first administration of the ASBTI.

110. The method of any of claims 69-109, wherein the administration of the ASBTI results in serum ALT concentration decreasing by at least about 10% relative to baseline.

111. The method of any of claims 69-110, wherein the subject has biliary atresia or intrahepatic cholestasis of pregnancy.

112. The method of any of claims 69-111, wherein the subject has PFIC 2.

Fig. 1

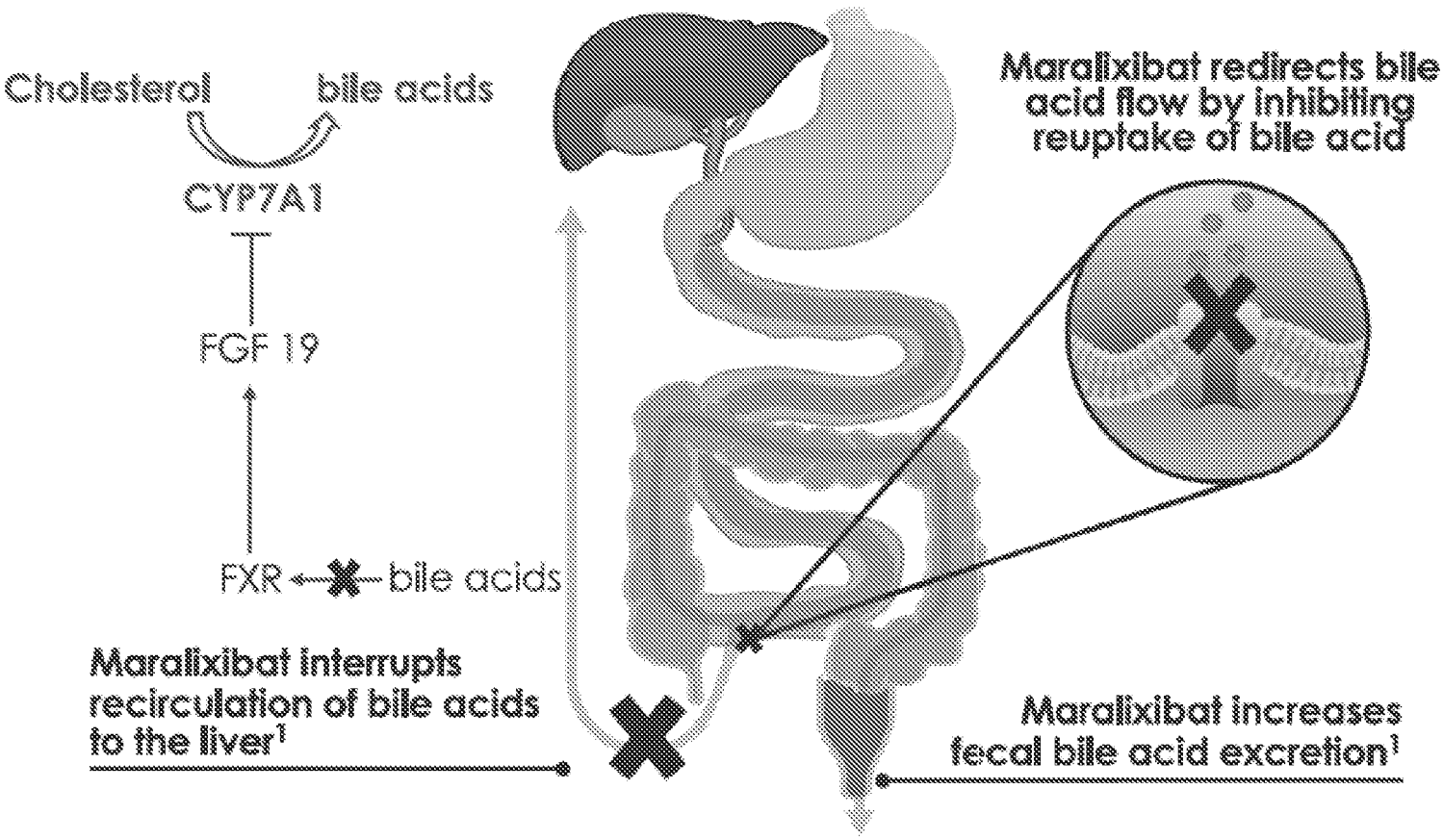

Cholesterol
bile acids
CYP7A1
FGF 19
FXR
bile acids
Maralixibat redirects bile acid flow by inhibiting reuptake of bile acid
Maralixibat interrupts recirculation of bile acids to the liver[1]
Maralixibat increases fecal bile acid excretion[1]

Fig. 2

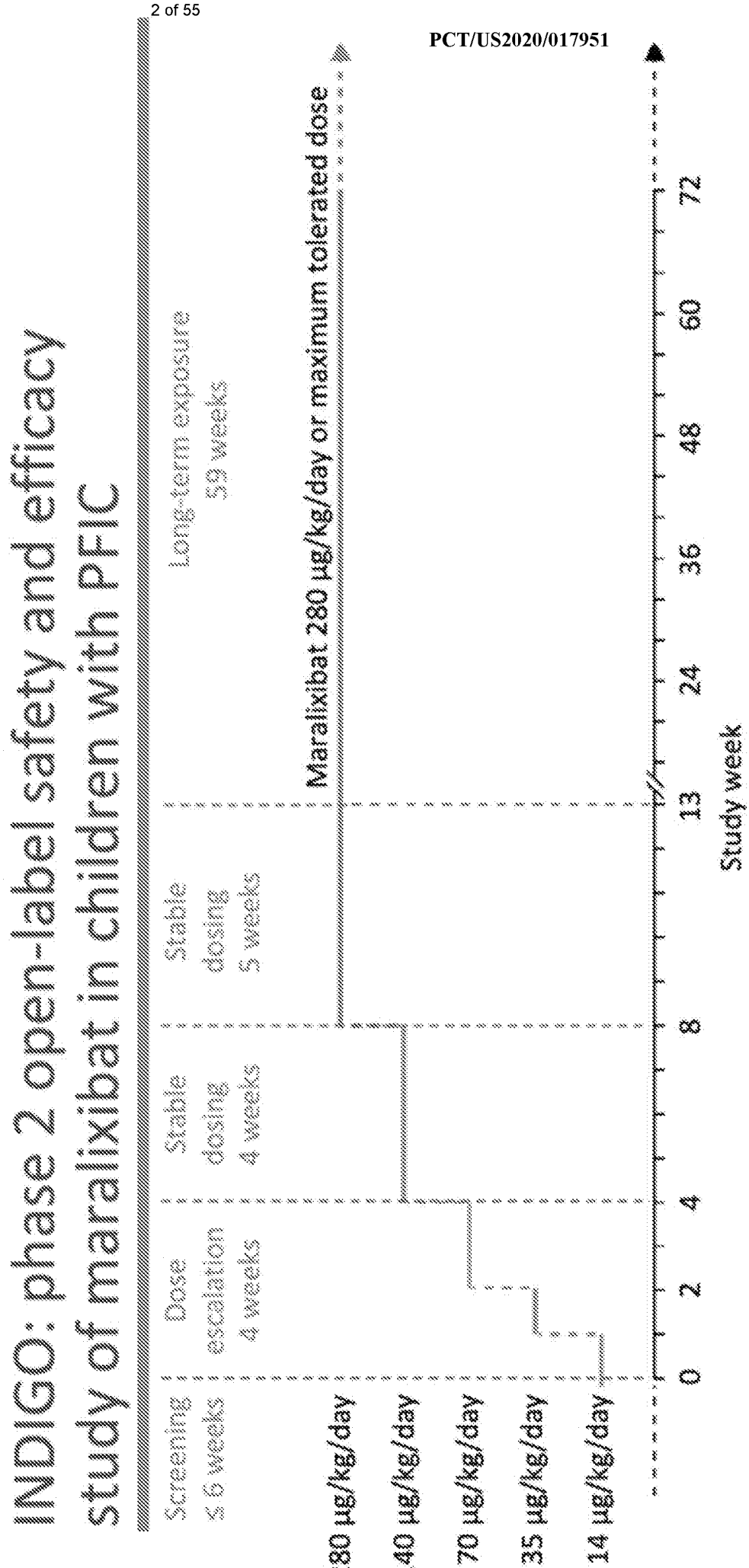

INDIGO: phase 2 open-label safety and efficacy study of maralixibat in children with PFIC
Screening ≤ 6 weeks
Dose escalation 4 weeks
Stable dosing 4 weeks
Stable dosing 5 weeks
Long-term exposure 59 weeks
Maralixibat 280 µg/kg/day or maximum tolerated dose
280 µg/kg/day
140 µg/kg/day
70 µg/kg/day
35 µg/kg/day
14 µg/kg/day
0
2
4
8
13
24
36
48
60
72
Study week

Fig. 3A

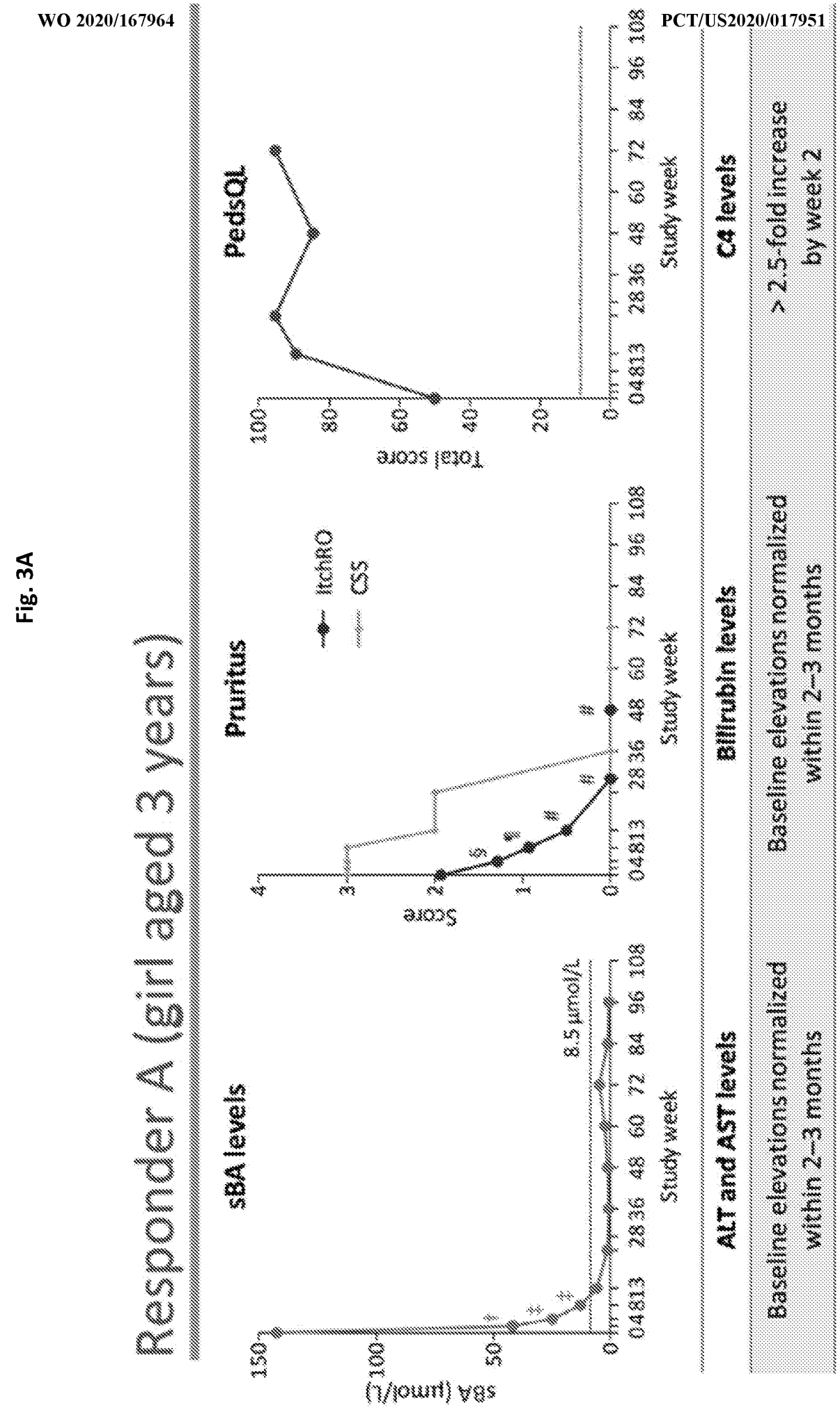

Responder A (girl aged 3 years)
sBA levels
sBA (µmol/L)
150
100
50
0
8.5 µmol/L
†
‡
0 4 8 13 28 36 48 60 72 84 96 108
Study week
Pruritus
Score
4
3
2
1
0
ItchRO
CSS
§
¶
#
0 4 8 13 28 36 48 60 72 84 96 108
Study week
PedsQL
Total score
100
80
60
40
20
0
0 4 8 13 28 36 48 60 72 84 96 108
Study week
ALT and AST levels
Baseline elevations normalized within 2–3 months
Bilirubin levels
Baseline elevations normalized within 2–3 months
C4 levels
> 2.5-fold increase by week 2
† ≥ 70%; ‡ ≥ 80% reduction from baseline
§ ≥ 0.5; ¶ ≥ 1.0; # ≥ 1.33 point reduction from baseline

Fig. 3B

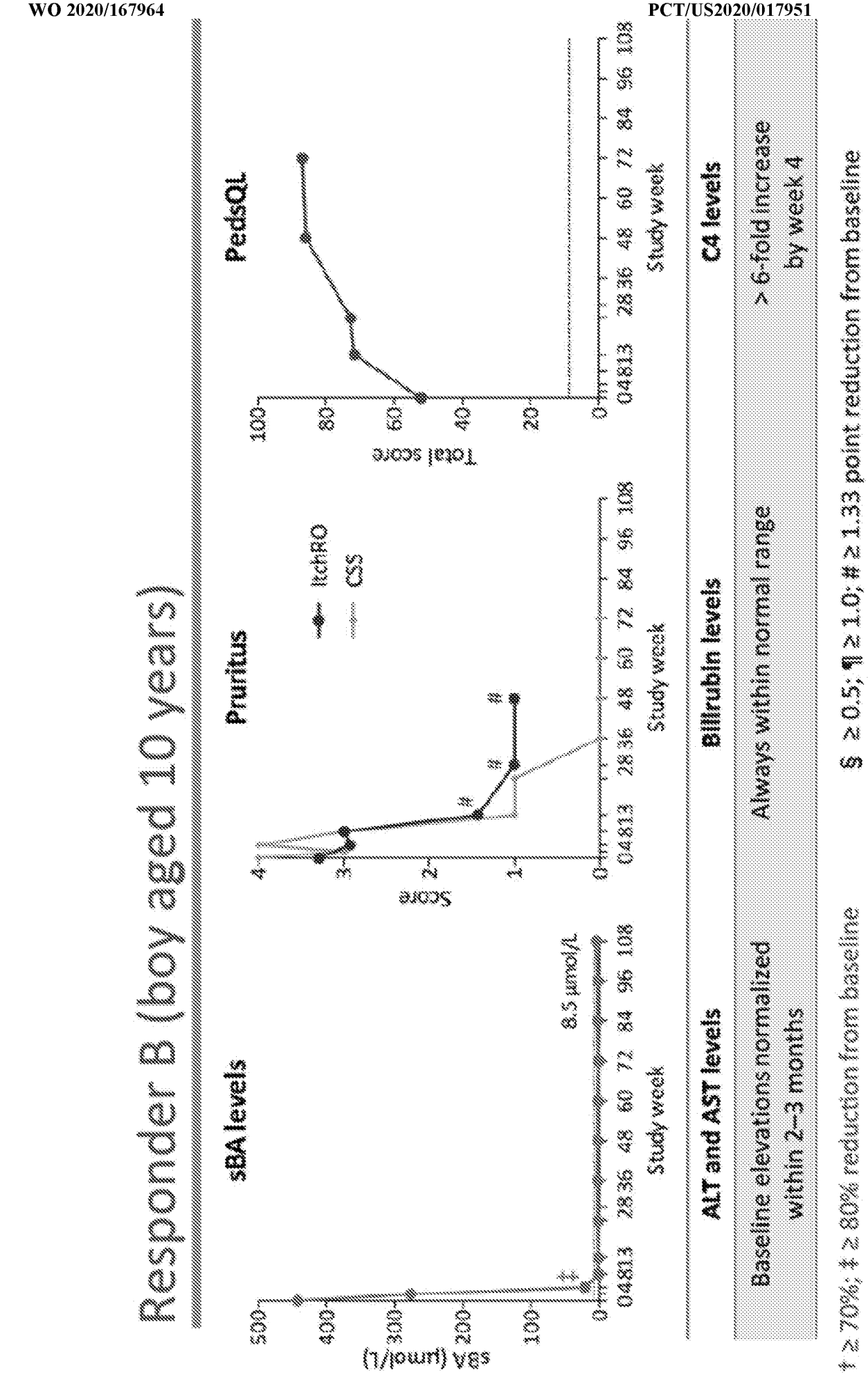

Responder B (boy aged 10 years)
sBA levels
sBA (µmol/L)
8.5 µmol/L
Study week
Pruritus
ItchRO
CSS
Score
Study week
PedsQL
Total score
Study week
ALT and AST levels
Baseline elevations normalized within 2–3 months
Bilirubin levels
Always within normal range
C4 levels
> 6-fold increase by week 4
† ≥ 70%; ‡ ≥ 80% reduction from baseline
§ ≥ 0.5; ¶ ≥ 1.0; # ≥ 1.33 point reduction from baseline

Fig. 3C

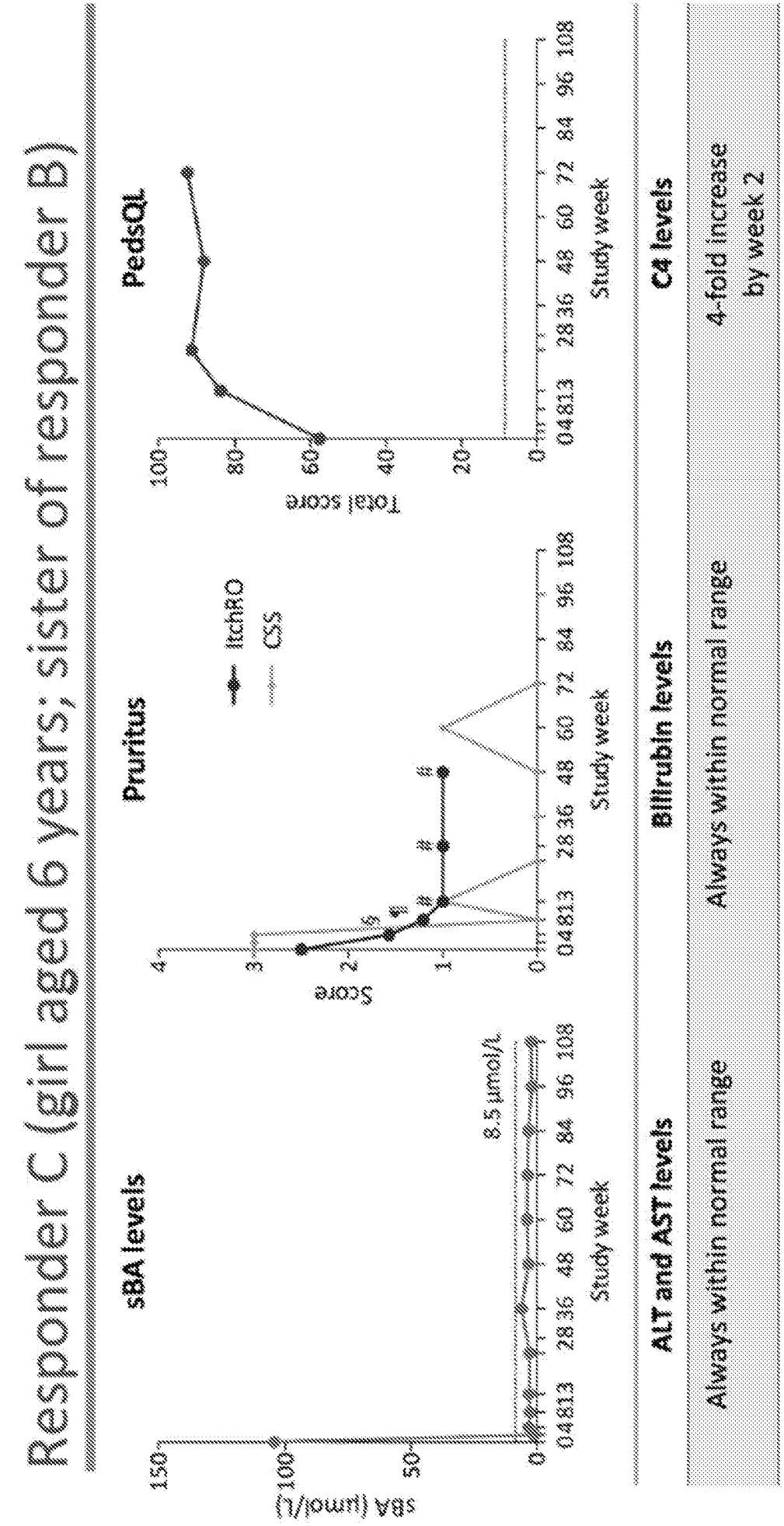

Responder C (girl aged 6 years; sister of responder B)
sBA levels
sBA (µmol/L)
150
100
50
0
8.5 µmol/L
0 4 8 13 28 36 48 60 72 84 96 108
Study week
Pruritus
Score
4
3
2
1
0
ItchRO
CSS
§
¶
#
0 4 8 13 28 36 48 60 72 84 96 108
Study week
PedsQL
Total score
100
80
60
40
20
0
0 4 8 13 28 36 48 60 72 84 96 108
Study week
ALT and AST levels
Always within normal range
Bilirubin levels
Always within normal range
C4 levels
4-fold increase by week 2
† ≥ 70%; ‡ ≥ 80% reduction from baseline
§ ≥ 0.5; ¶ ≥ 1.0; # ≥ 1.33 point reduction from baseline

Fig. 3D

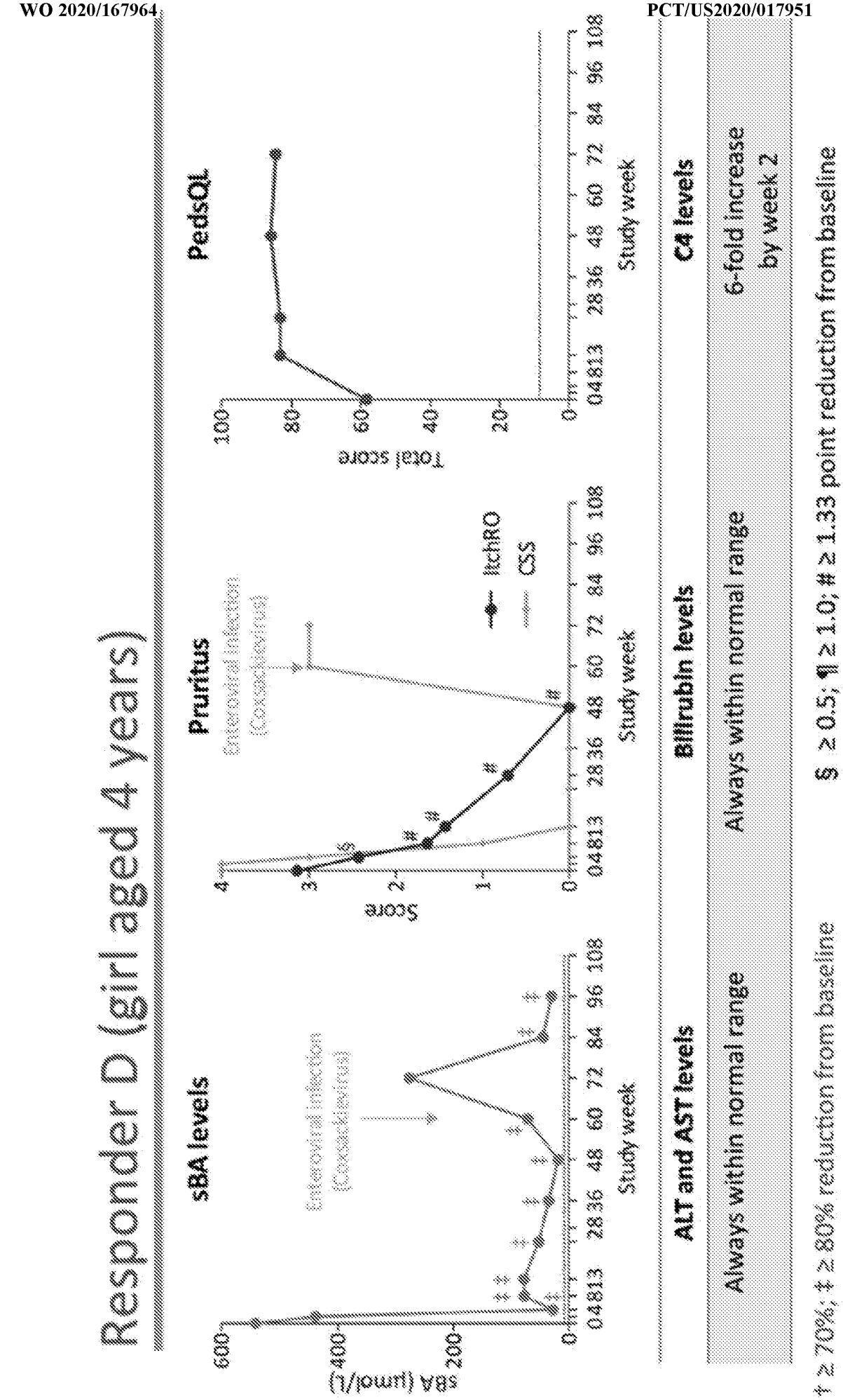

Responder D (girl aged 4 years)
sBA levels
sBA (µmol/L)
600
400
200
0
Enterovirial infection
(Coxsackievirus)
04 8 13 28 36 48 60 72 84 96 108
Study week
Pruritus
Score
4
3
2
1
0
Enterovirial infection
(Coxsackievirus)
ItchRO
CSS
04 8 13 28 36 48 60 72 84 96 108
Study week
PedsQL
Total score
100
80
60
40
20
0
04 8 13 28 36 48 60 72 84 96 108
Study week
ALT and AST levels
Always within normal range
Bilirubin levels
Always within normal range
C4 levels
6-fold increase
by week 2
† ≥ 70%; ‡ ≥ 80% reduction from baseline
§ ≥ 0.5; ¶ ≥ 1.0; # ≥ 1.33 point reduction from baseline

Fig. 3E

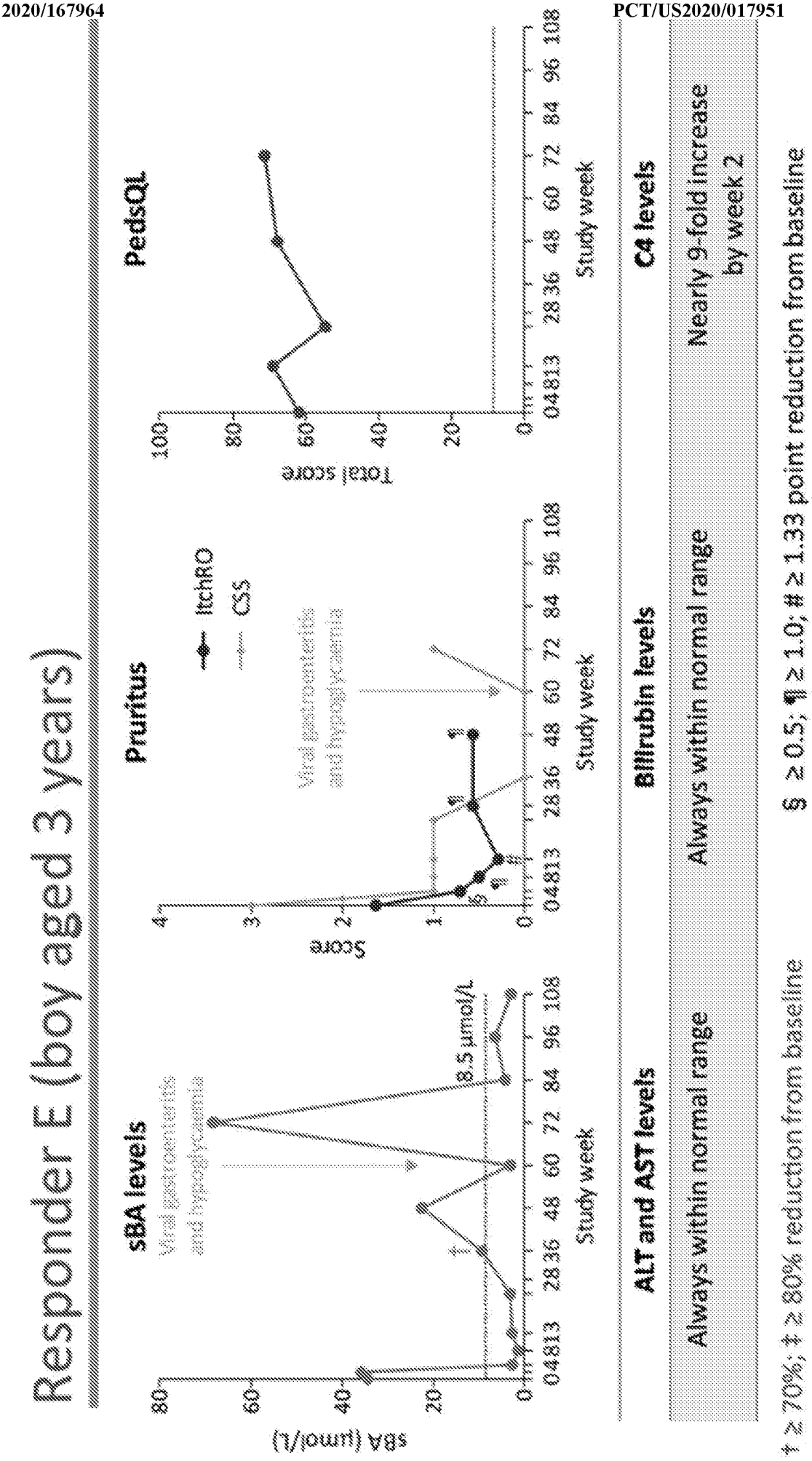
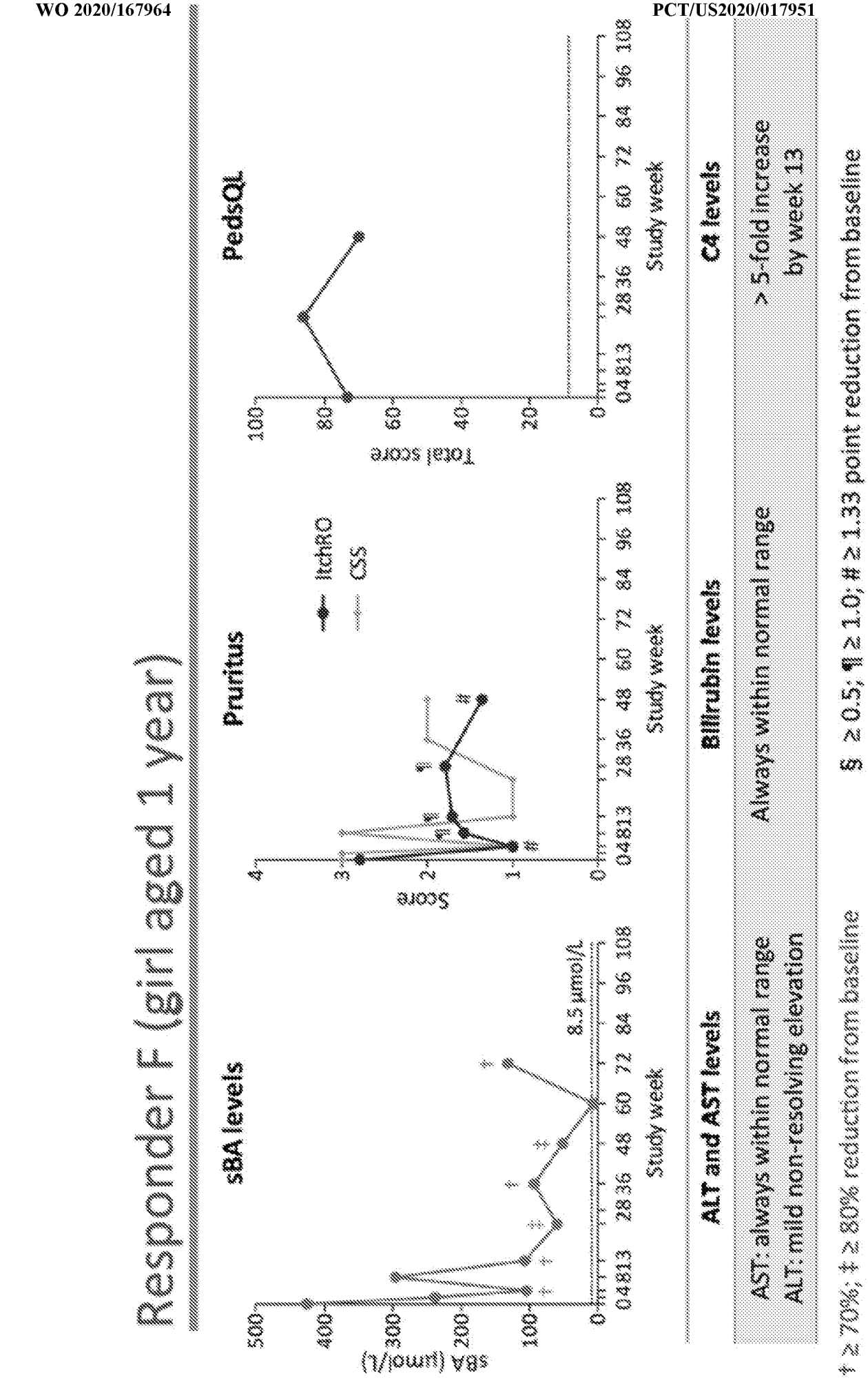

Responder E (boy aged 3 years)
sBA levels
Viral gastroenteritis and hypoglycaemia
8.5 µmol/L
sBA (µmol/L)
Study week
Pruritus
ItchRO
CSS
Viral gastroenteritis and hypoglycaemia
Score
Study week
PedsQL
Total score
Study week
ALT and AST levels
Always within normal range
Bilirubin levels
Always within normal range
C4 levels
Nearly 9-fold increase by week 2
† ≥ 70%; ‡ ≥ 80% reduction from baseline
§ ≥ 0.5; ¶ ≥ 1.0; # ≥ 1.33 point reduction from baseline

Fig. 3F


Responder F (girl aged 1 year)
sBA levels
sBA (umol/L)
8.5 µmol/L
Study week
Pruritus
Score
ItchRO
CSS
Study week
PedsQL
Total score
Study week
ALT and AST levels
AST: always within normal range
ALT: mild non-resolving elevation
Bilirubin levels
Always within normal range
C4 levels
> 5-fold increase by week 13
† ≥ 70%; ‡ ≥ 80% reduction from baseline
§ ≥ 0.5; ¶ ≥ 1.0; # ≥ 1.33 point reduction from baseline

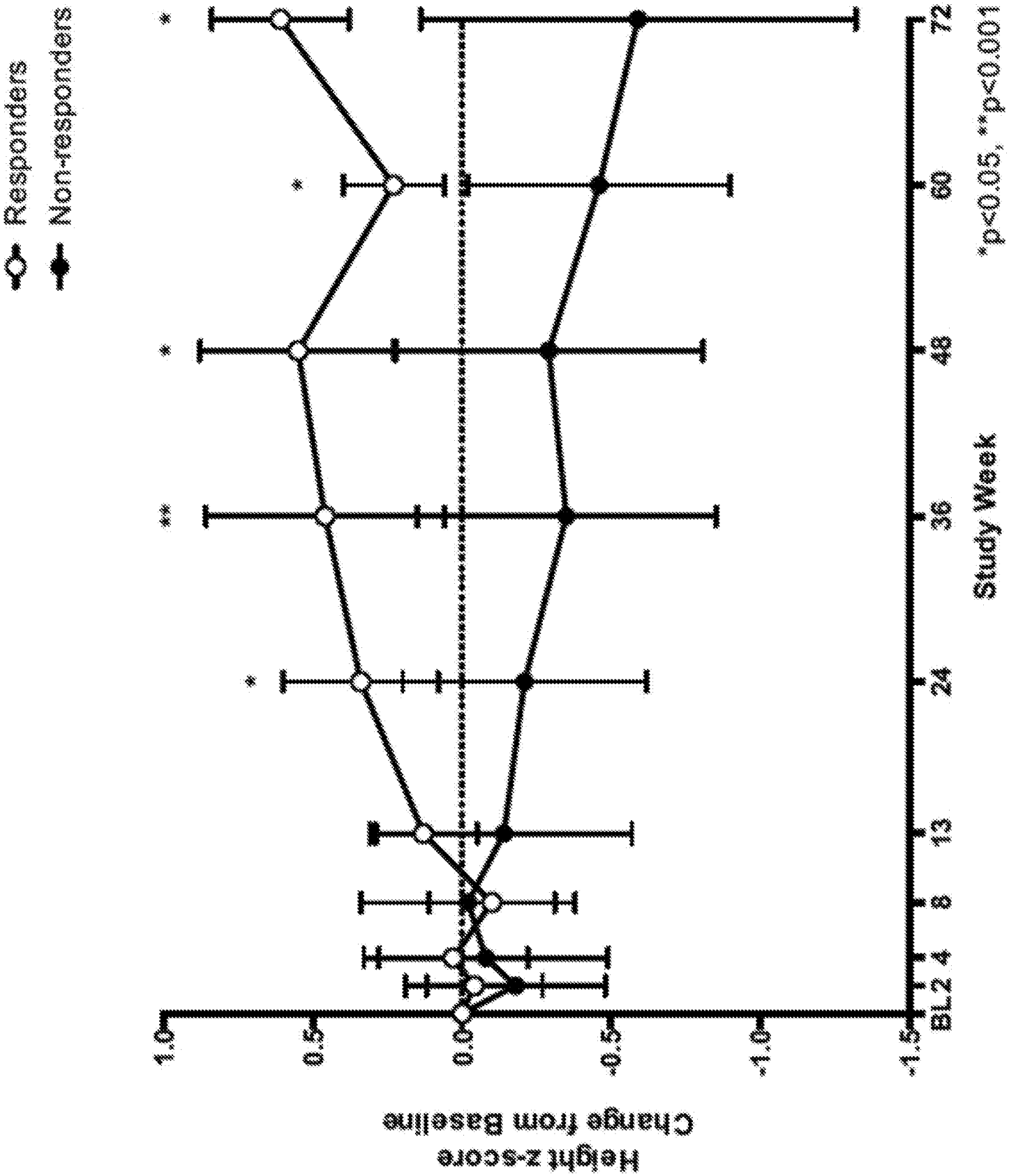
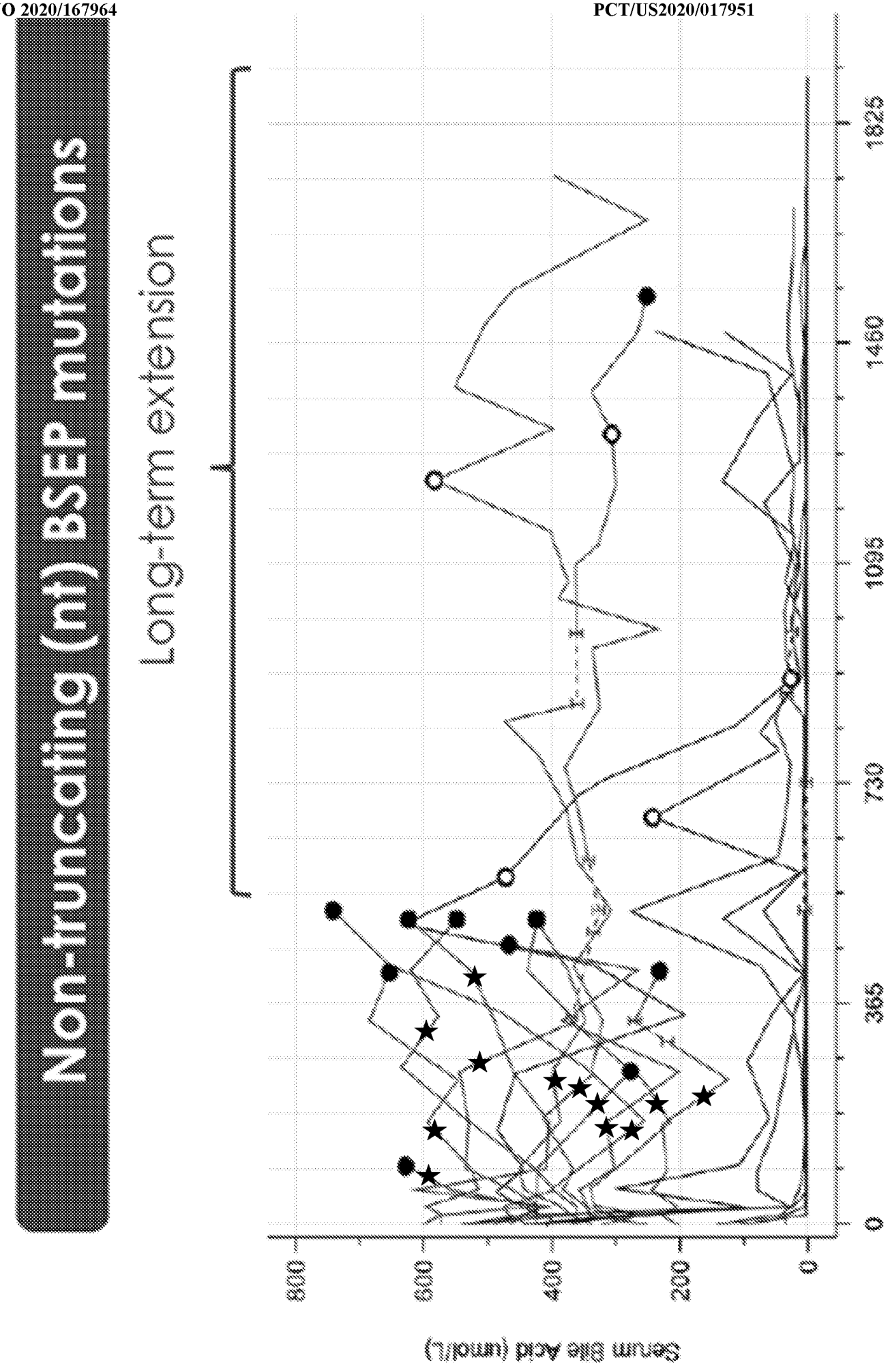

Responders
Non-responders
Height z-score
Change from Baseline
1.0
0.5
0.0
-0.5
-1.0
-1.5
BL 2 4 8 13 24 36 48 60 72
Study Week
*p<0.05, **p<0.001

Fig. 4

Fig. 5A


Non-truncating (nt) BSEP mutations
Long-term extension
Serum Bile Acid (umol/L)
800
600
400
200
0
0
365
730
1095
1460
1825

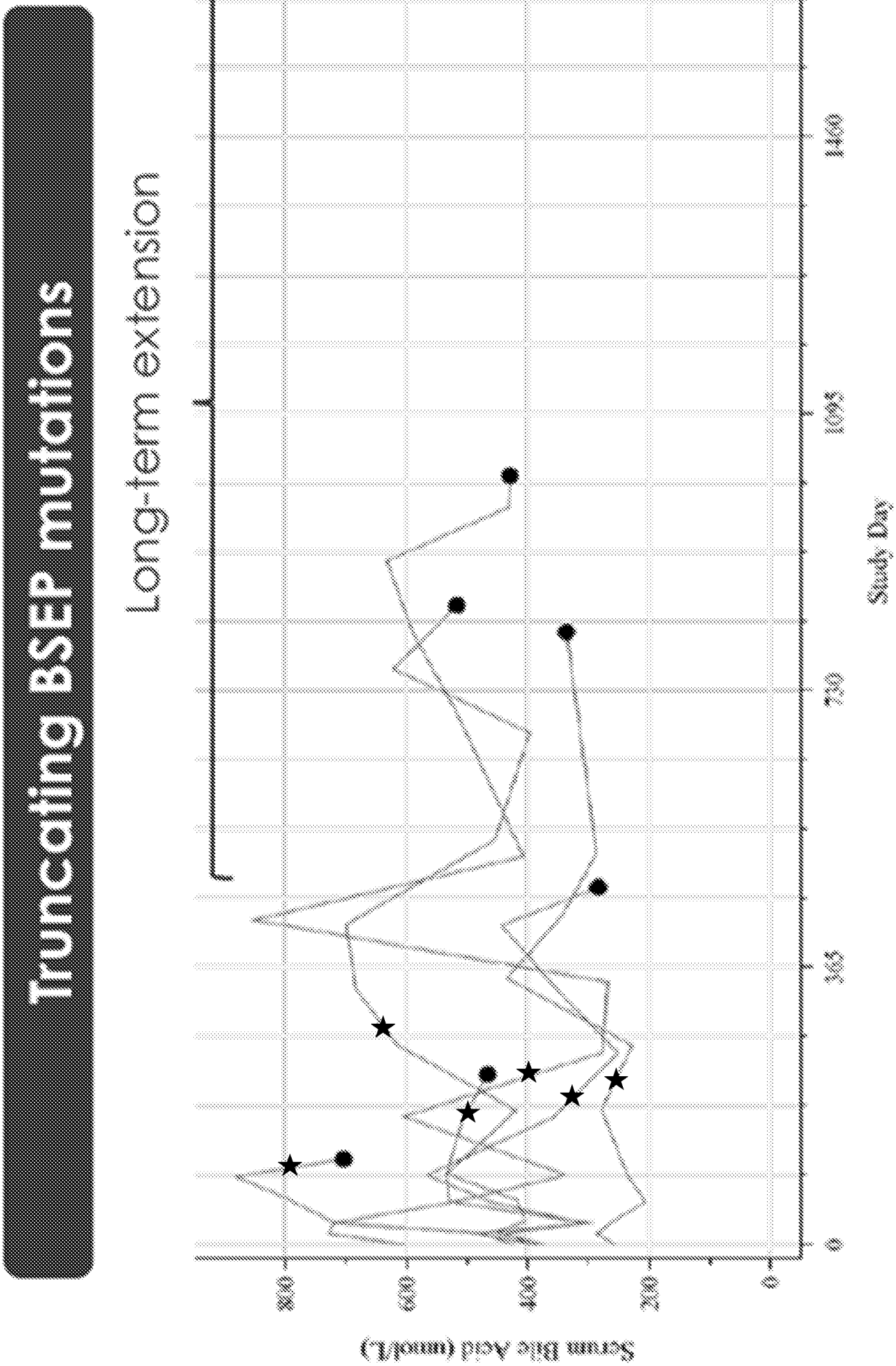

Truncating BSEP mutations
Long-term extension
Serum Bile Acid (umol/L)
800
600
400
200
0
Study Day
0
365
730
1095
1460

Fig. 5B

Fig. 6

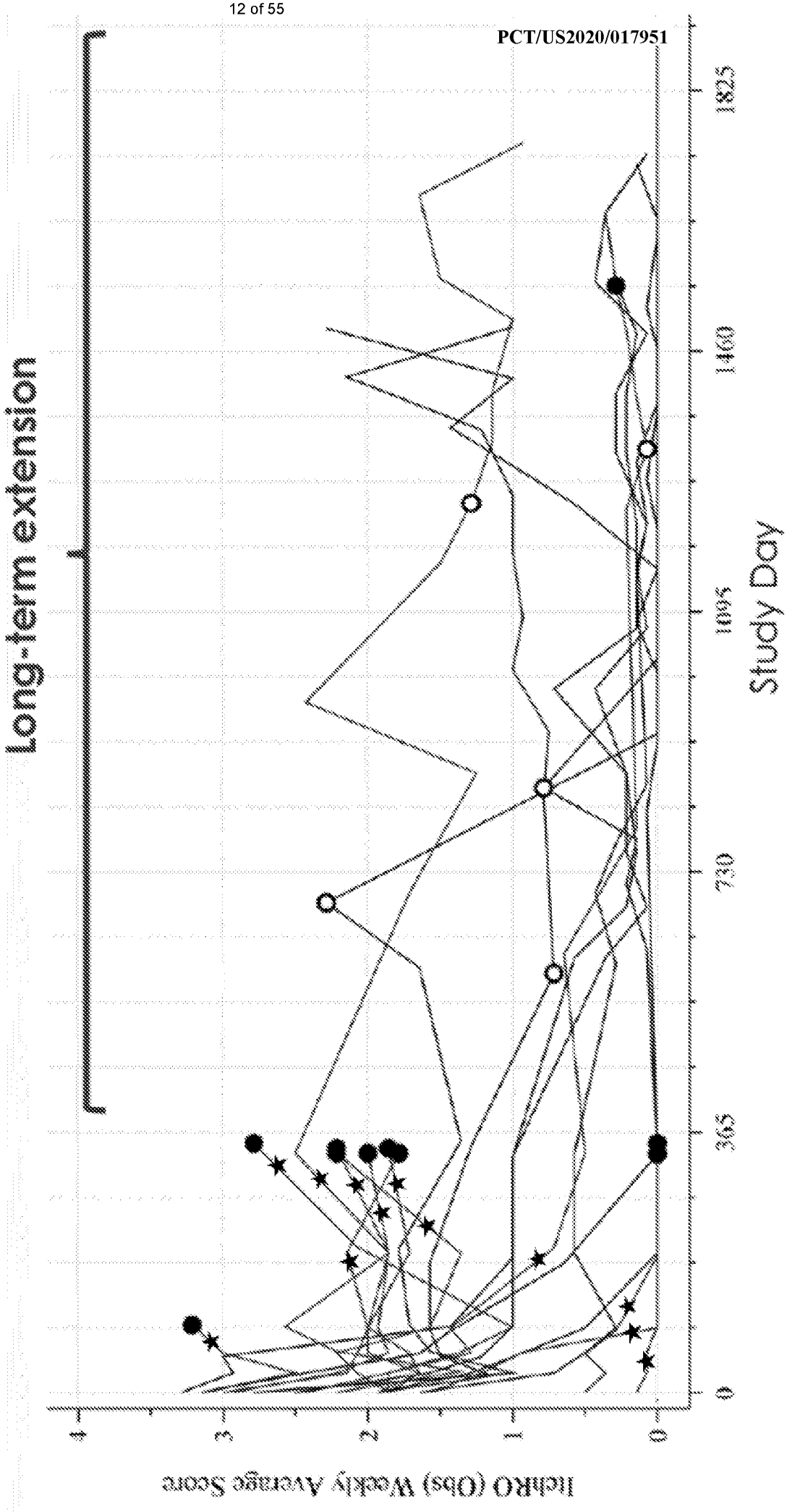

Long-term extension
ItchRO (Obs) Weekly Average Score
0
1
2
3
4
0
365
730
1095
1460
1825
Study Day

Fig. 7

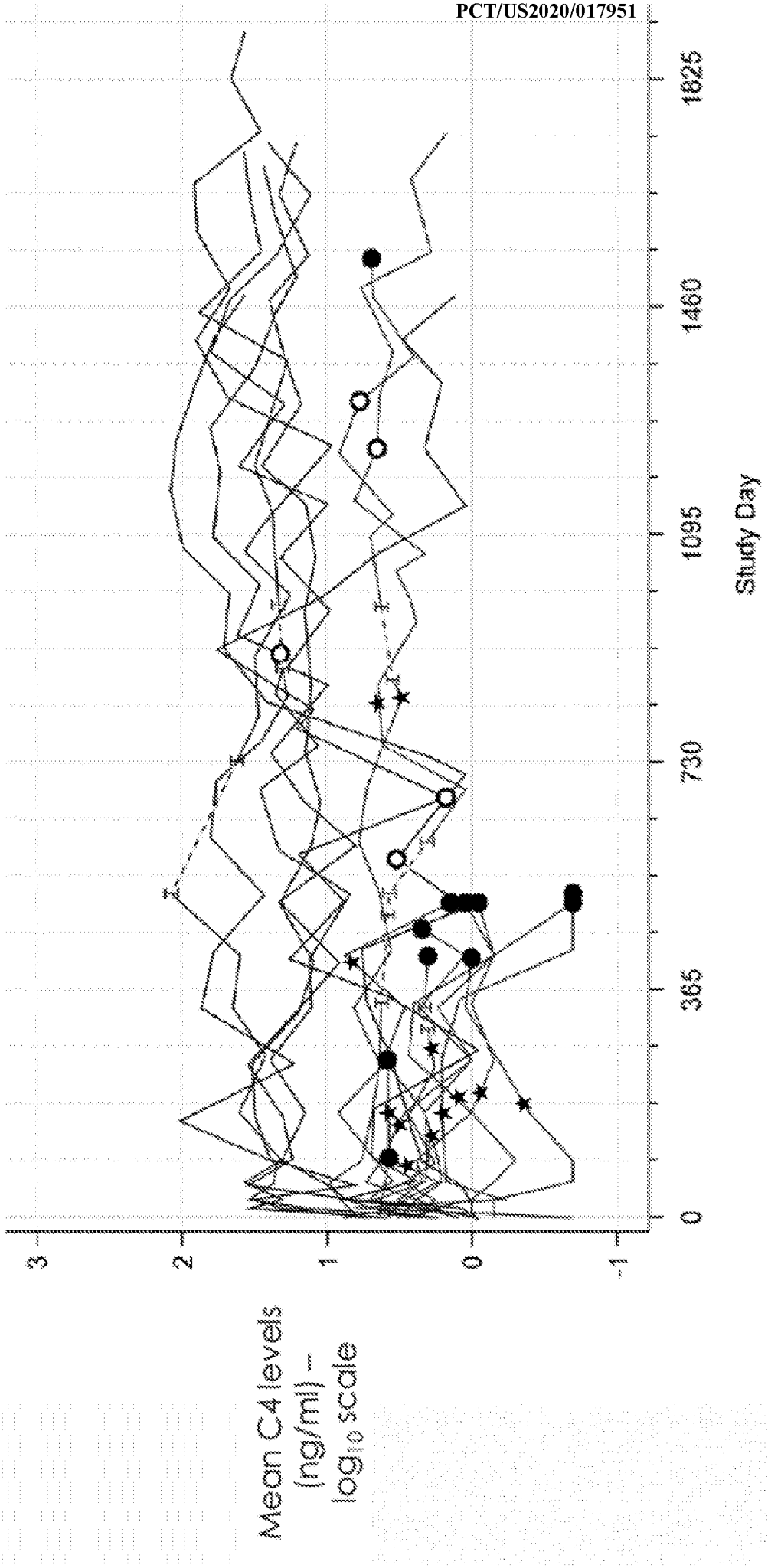

Mean C4 levels (ng/ml) – log10 scale
3
2
1
0
-1
0
365
730
1095
1460
1825
Study Day

Fig. 8

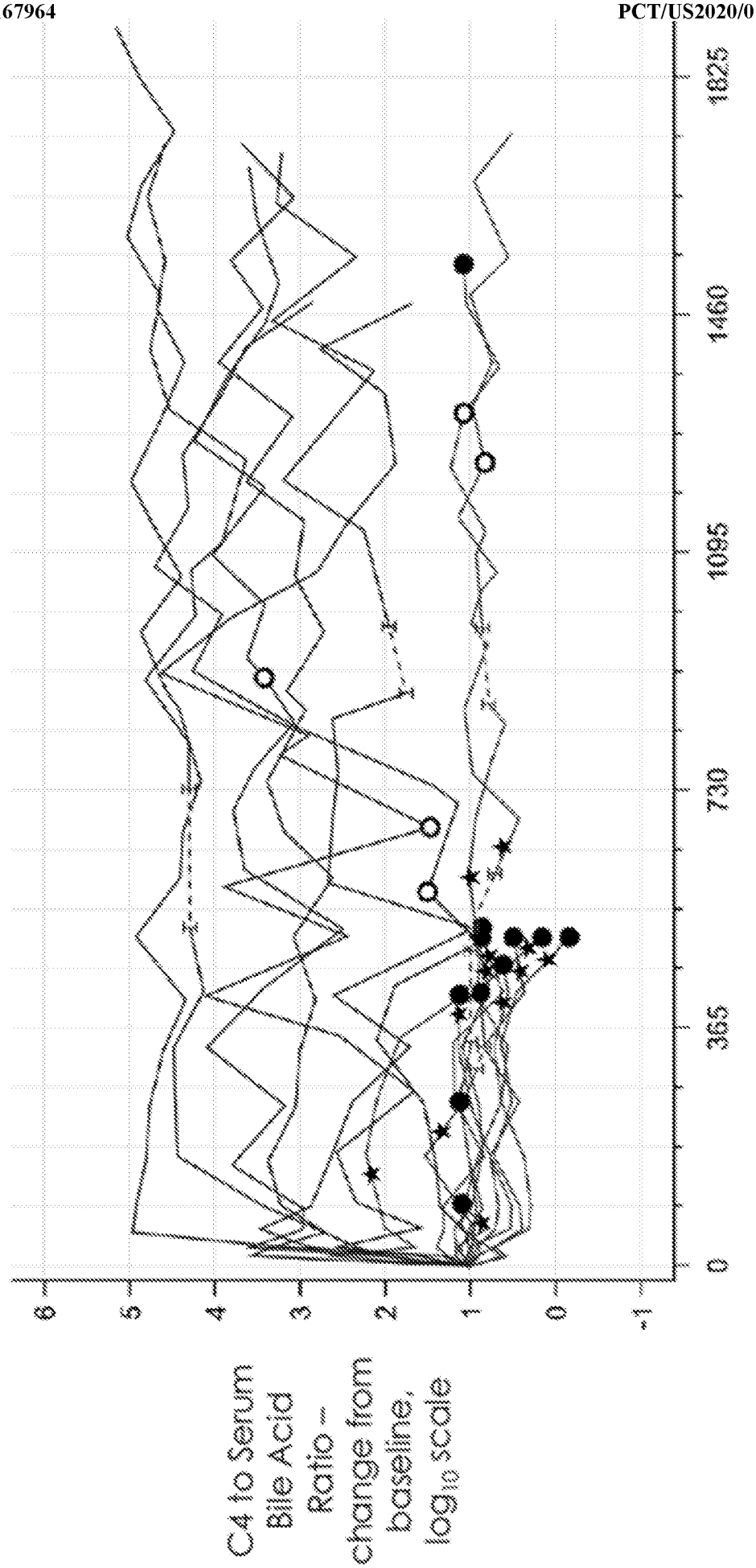

C4 to Serum Bile Acid Ratio – change from baseline, log10 scale
6
5
4
3
2
1
0
-1
0
365
730
1095
1460
1825

Fig. 9

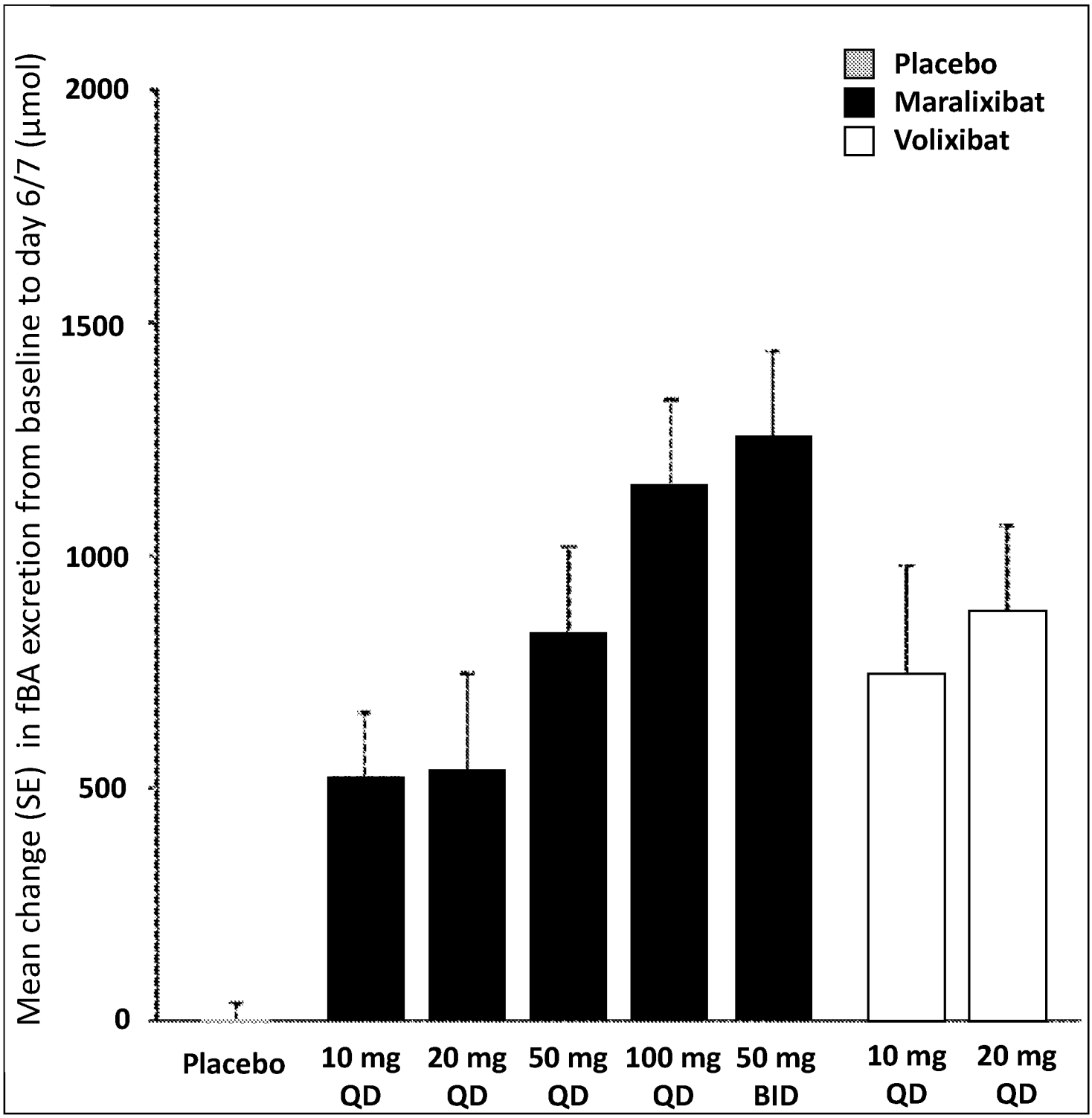

Placebo
Maralixibat
Volixibat
Mean change (SE) in fBA excretion from baseline to day 6/7 (µmol)
2000
1500
1000
500
0
Placebo
10 mg QD
20 mg QD
50 mg QD
100 mg QD
50 mg BID
10 mg QD
20 mg QD

Fig. 10

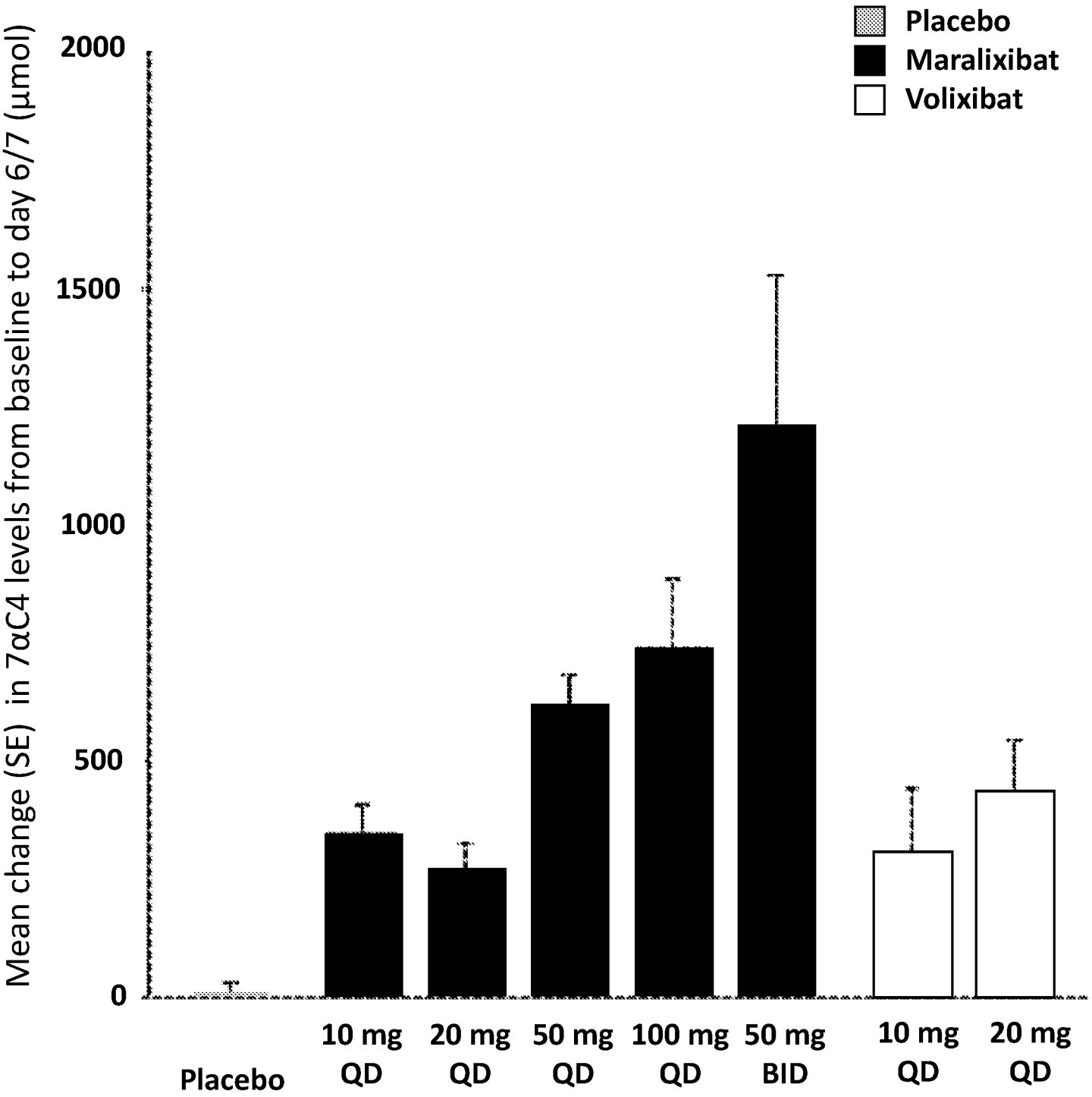

Placebo
Maralixibat
Volixibat
Mean change (SE) in 7αC4 levels from baseline to day 6/7 (µmol)
2000
1500
1000
500
0
Placebo
10 mg QD
20 mg QD
50 mg QD
100 mg QD
50 mg BID
10 mg QD
20 mg QD

Fig. 11

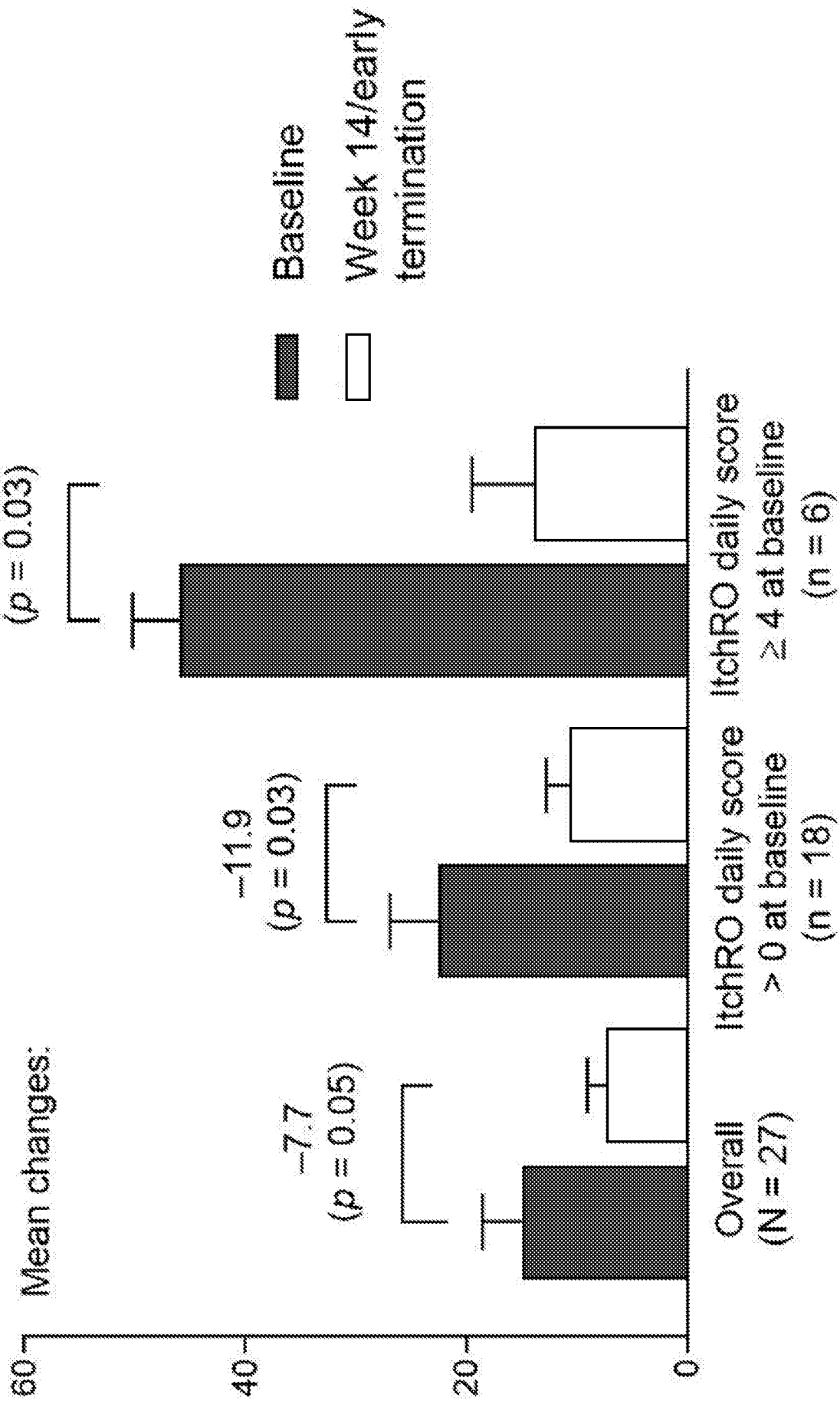
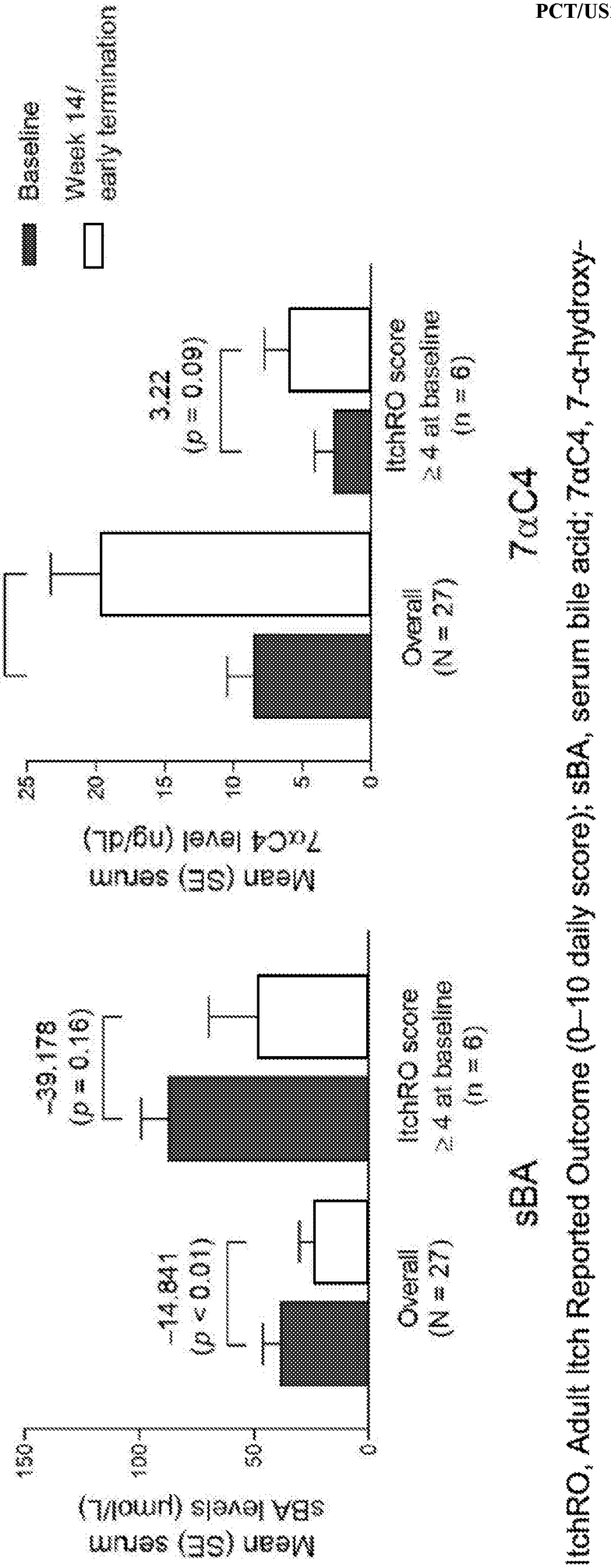

Mean (SE) ItchRO weekly sum score
60
40
20
0
Baseline
Week 14/early termination
Mean changes:
−7.7 (p = 0.05)
−11.9 (p = 0.03)
−32.2 (p = 0.03)
Overall (N = 27)
ItchRO daily score > 0 at baseline (n = 18)
ItchRO daily score ≥ 4 at baseline (n = 6)

Fig. 12



ItchRO, Adult Itch Reported Outcome (0–10 daily score); sBA, serum bile acid; 7αC4, 7-α-hydroxy-cholesten-3-one

Fig. 13

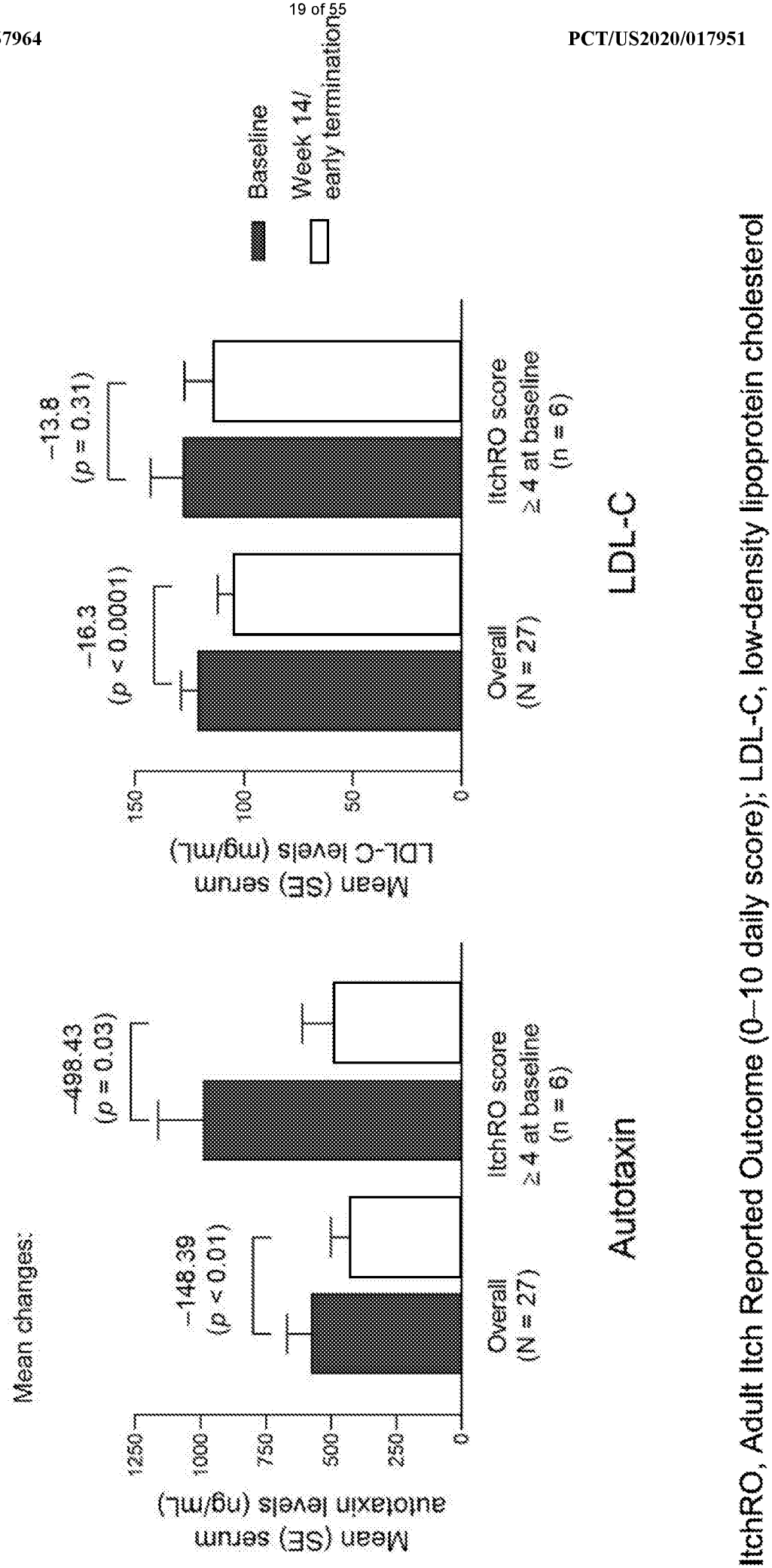

Mean changes:
Mean (SE) serum autotaxin levels (ng/mL)
1250
1000
750
500
250
0
−148.39 (p < 0.01)
−498.43 (p = 0.03)
Overall (N = 27)
ItchRO score ≥ 4 at baseline (n = 6)
Autotaxin
Mean (SE) serum LDL-C levels (mg/mL)
150
100
50
0
−16.3 (p < 0.0001)
−13.8 (p = 0.31)
Overall (N = 27)
ItchRO score ≥ 4 at baseline (n = 6)
LDL-C
Baseline
Week 14/ early termination
ItchRO, Adult Itch Reported Outcome (0–10 daily score); LDL-C, low-density lipoprotein cholesterol

Fig. 14

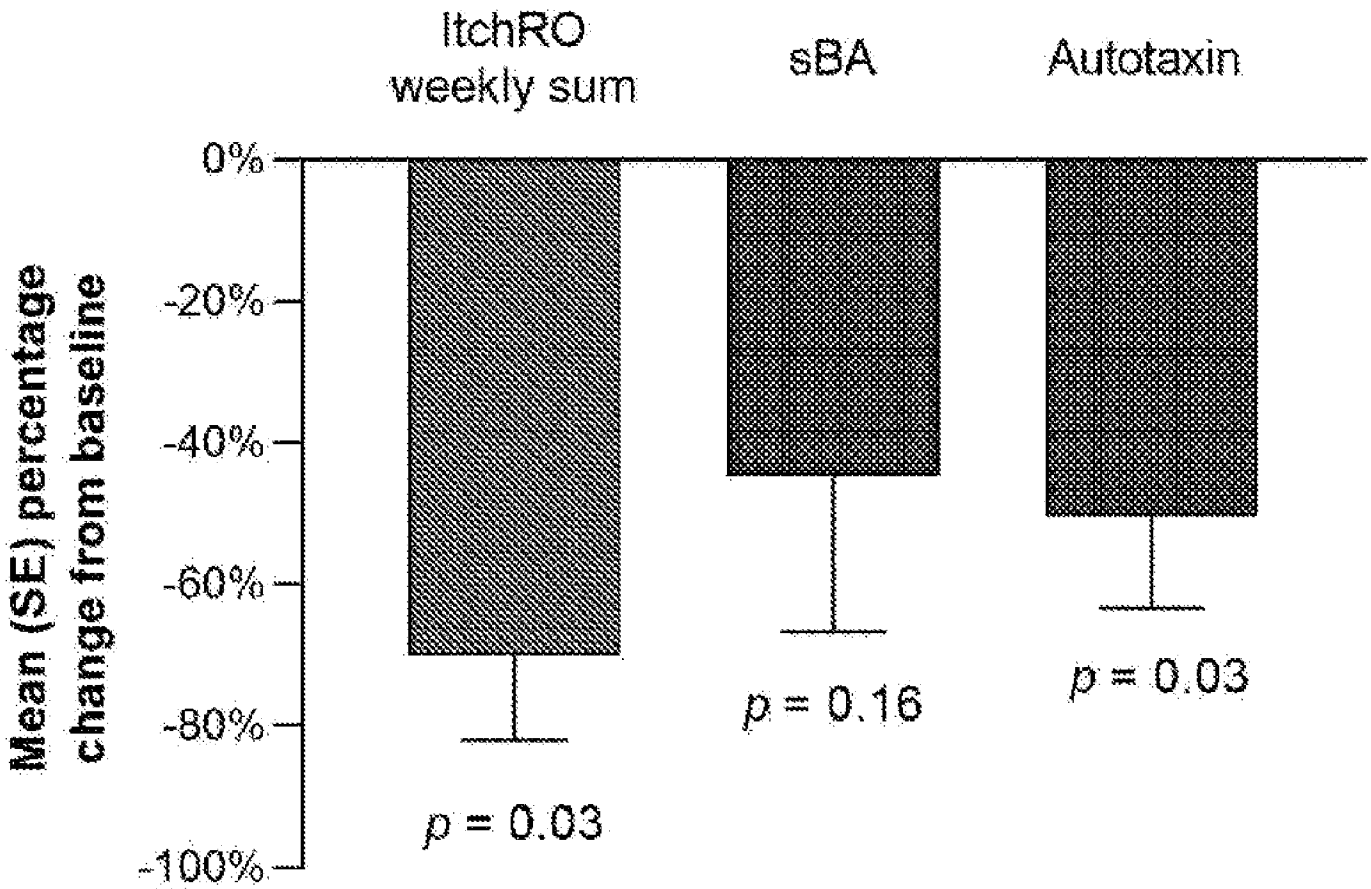

ItchRO weekly sum
sBA
Autotaxin
0%
-20%
-40%
-60%
-80%
-100%
Mean (SE) percentage change from baseline
p = 0.03
p = 0.16
p = 0.03

Fig. 15

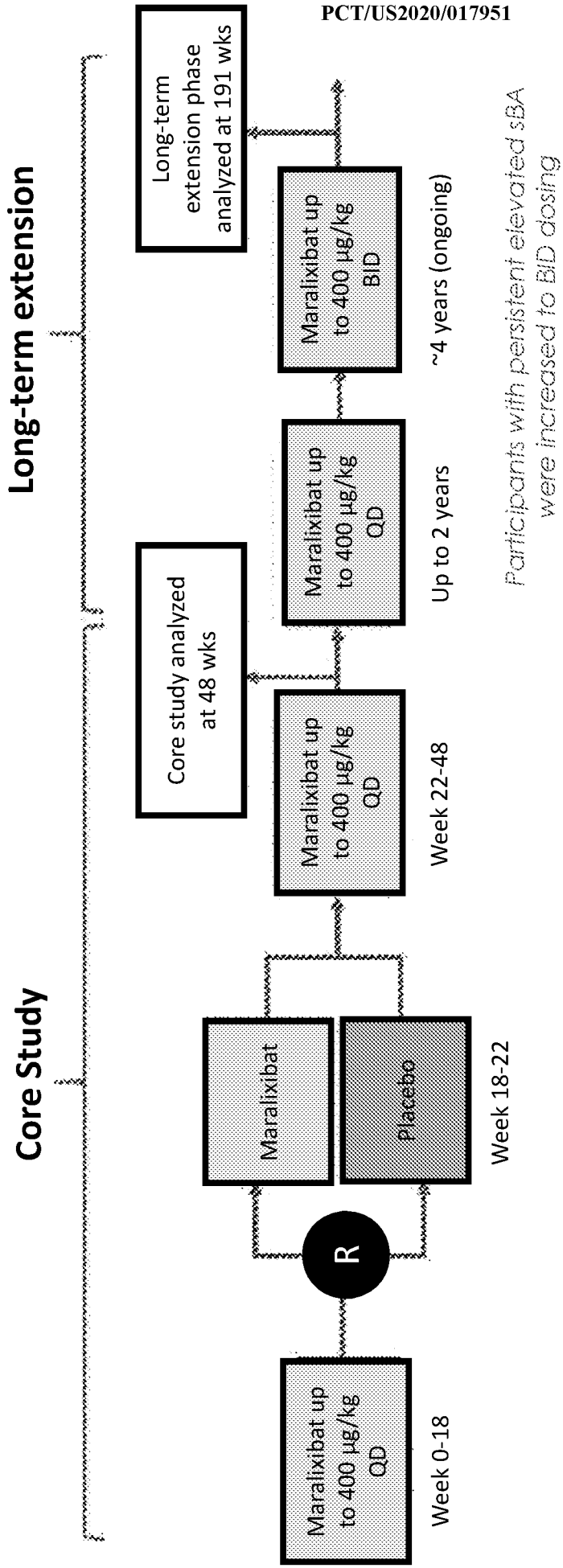

Core Study
Long-term extension
Maralixibat up to 400 µg/kg QD
Week 0-18
R
Maralixibat
Placebo
Week 18-22
Maralixibat up to 400 µg/kg QD
Week 22-48
Core study analyzed at 48 wks
Maralixibat up to 400 µg/kg QD
Up to 2 years
Maralixibat up to 400 µg/kg BID
~4 years (ongoing)
Long-term extension phase analyzed at 191 wks
Participants with persistent elevated sBA were increased to BID dosing

Fig. 16

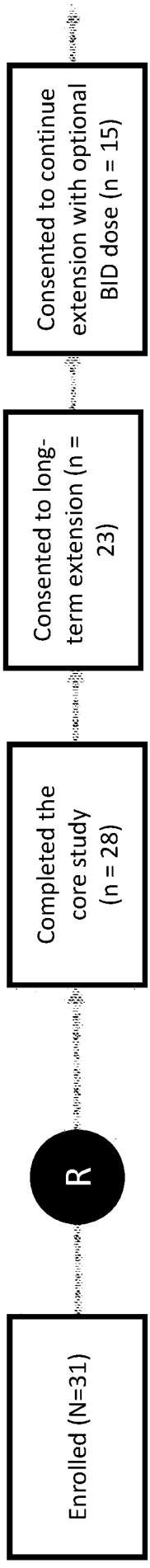
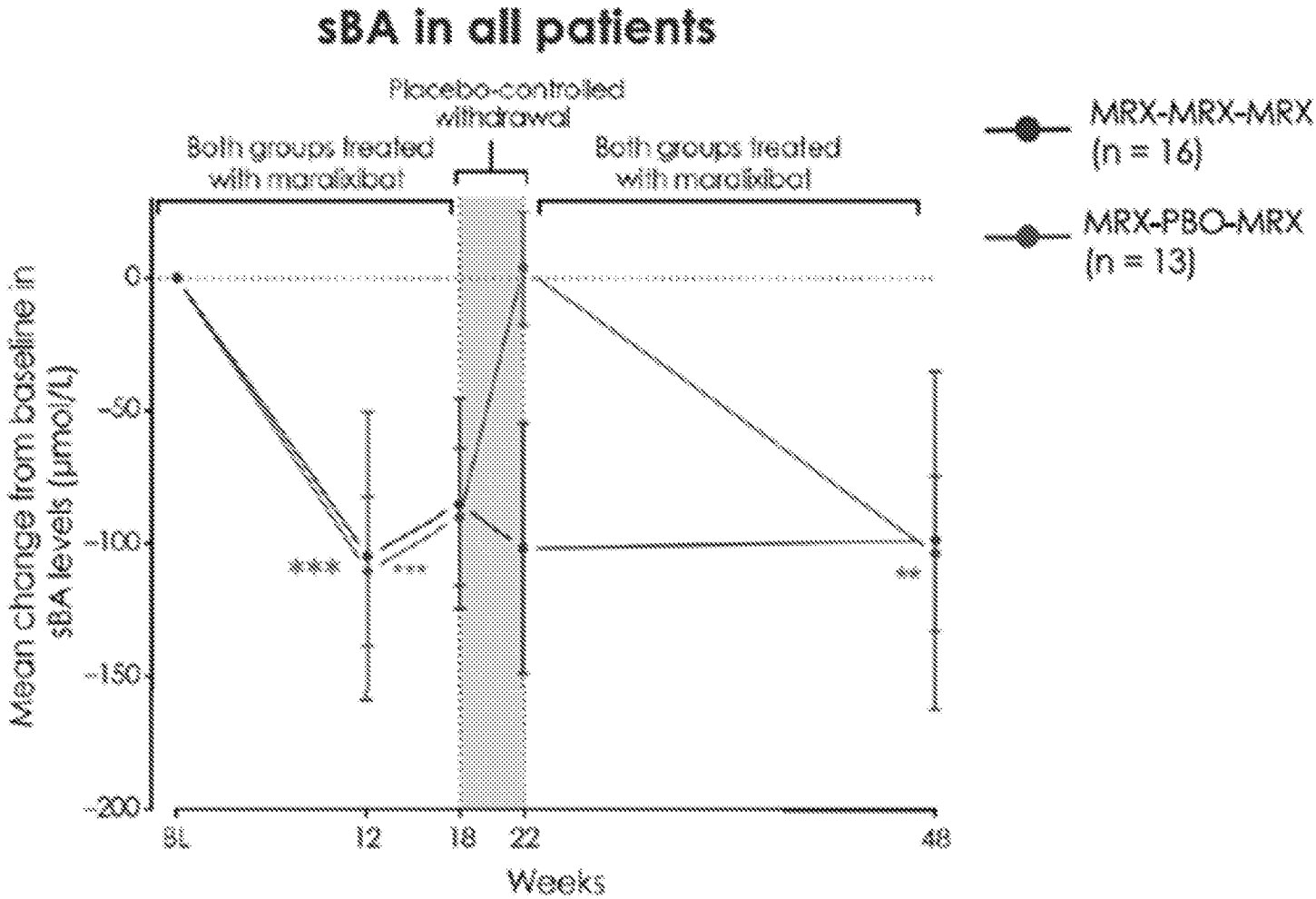

Enrolled (N=31)
R
Completed the core study (n = 28)
Consented to long-term extension (n = 23)
Consented to continue extension with optional BID dose (n = 15)

Fig. 17A



**p < 0.01, ***p < 0.001, change from baseline (overall population)

††p < 0.01, maralixibat versus placebo

Error bars show standard deviation

Fig. 17B

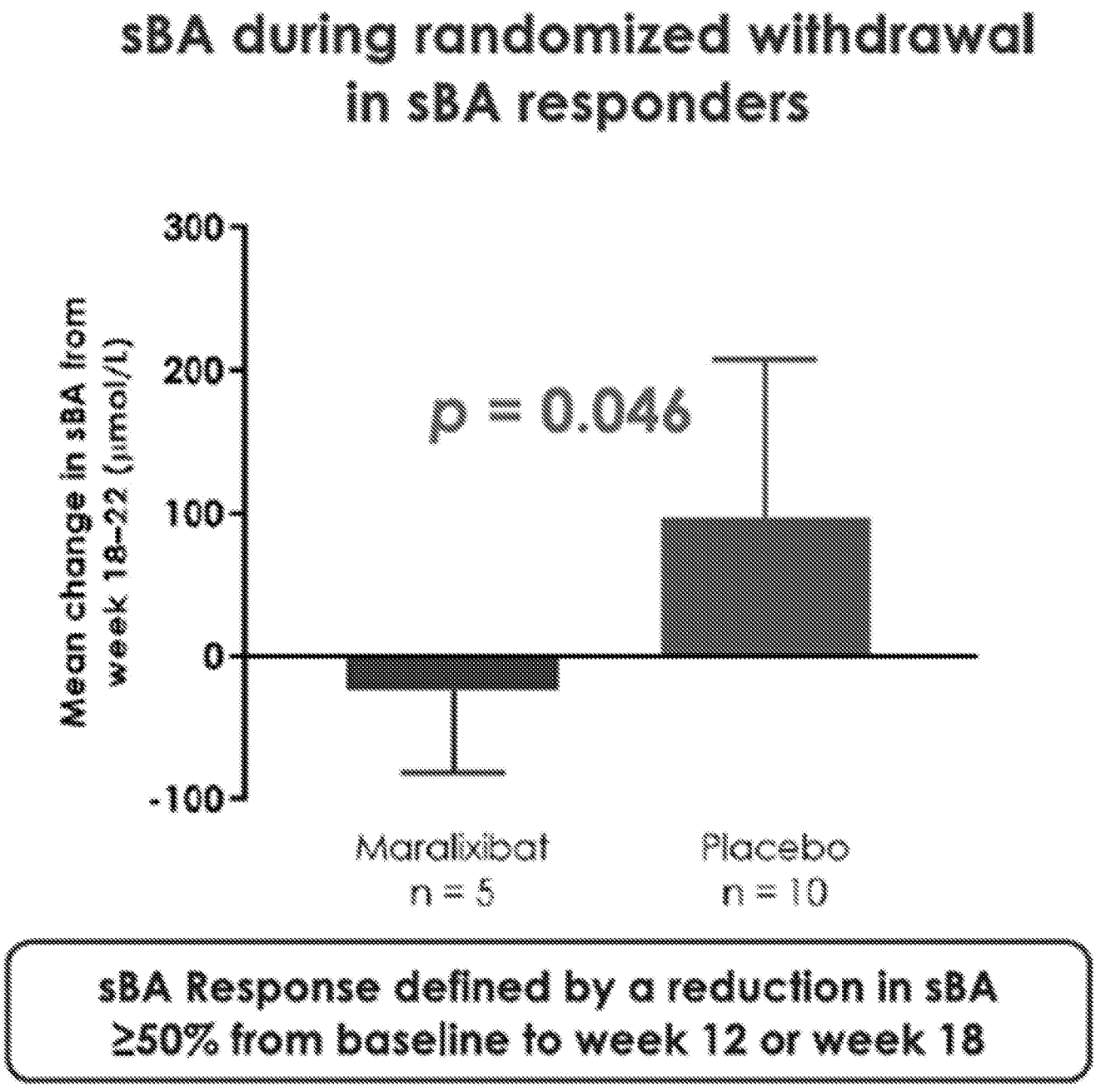
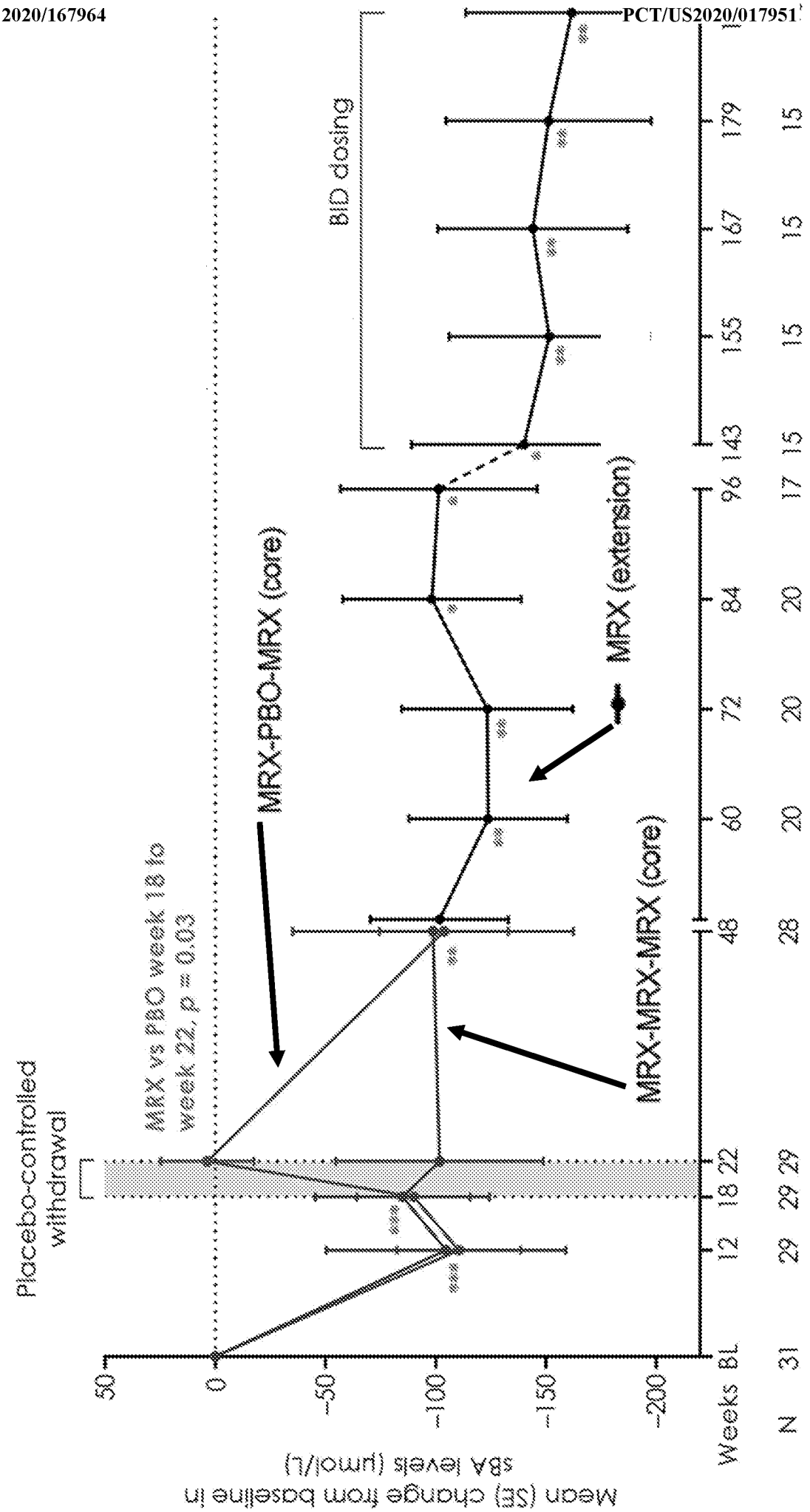

sBA during randomized withdrawal in sBA responders
Mean change in sBA from week 18–22 (µmol/L)
300
200
100
0
-100
p = 0.046
Maralixibat n = 5
Placebo n = 10
sBA Response defined by a reduction in sBA ≥50% from baseline to week 12 or week 18

Fig. 18



Change from baseline, * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$ (overall population)

Fig. 19

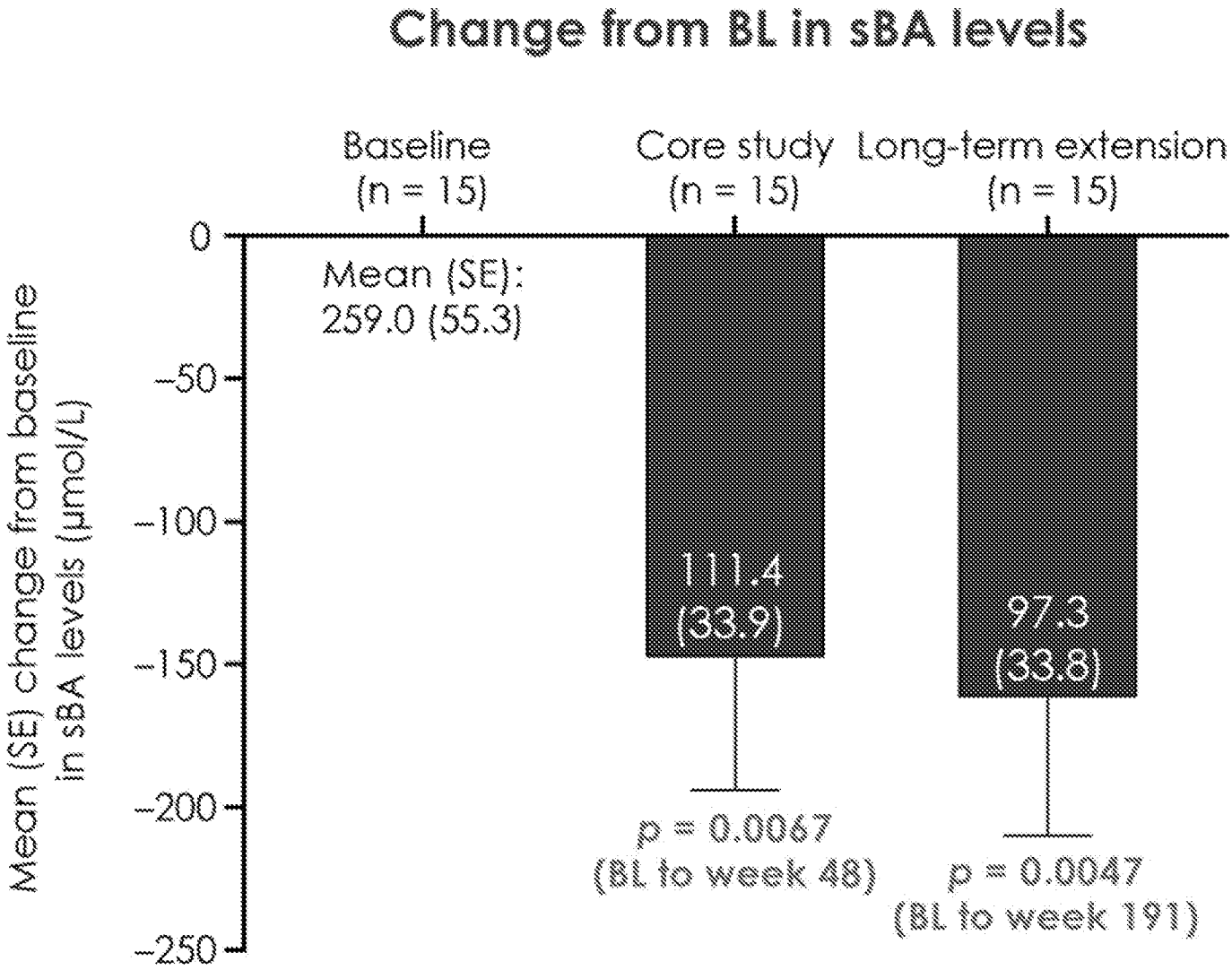
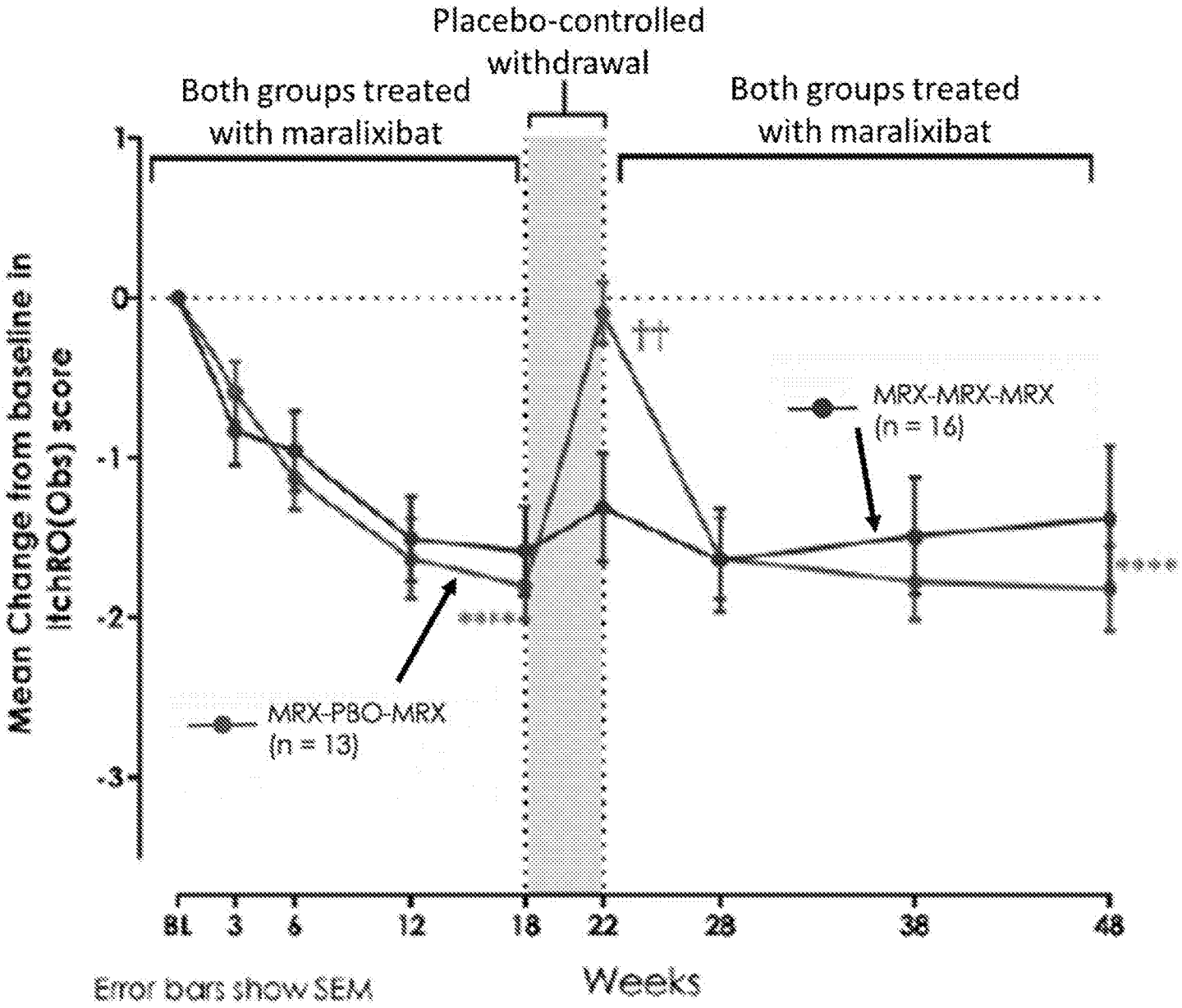
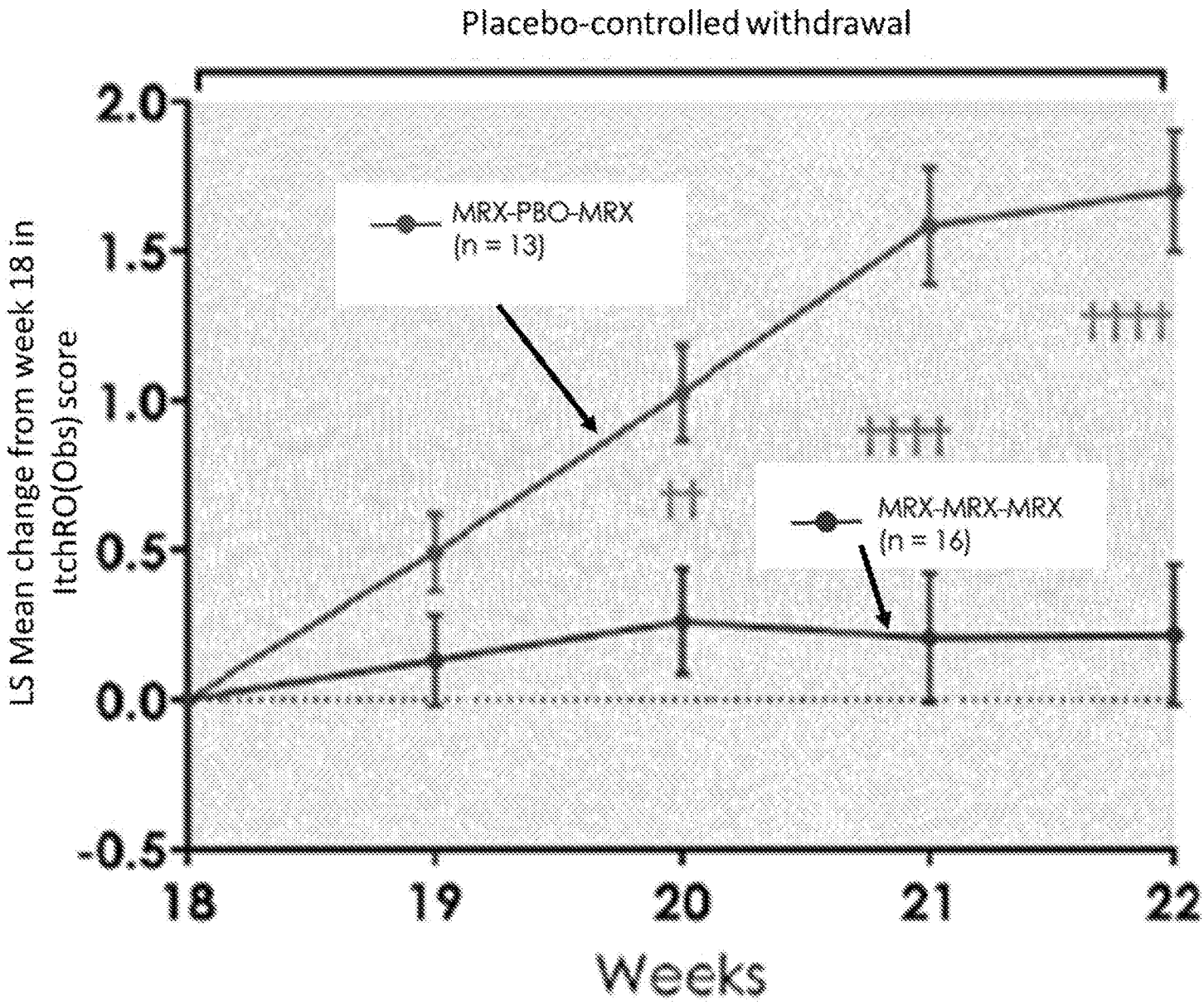

Change from BL in sBA levels
Baseline (n = 15)
Core study (n = 15)
Long-term extension (n = 15)
Mean (SE): 259.0 (55.3)
111.4 (33.9)
97.3 (33.8)
p = 0.0067 (BL to week 48)
p = 0.0047 (BL to week 191)
Mean (SE) change from baseline in sBA levels (µmol/L)
0
−50
−100
−150
−200
−250

Fig. 20A



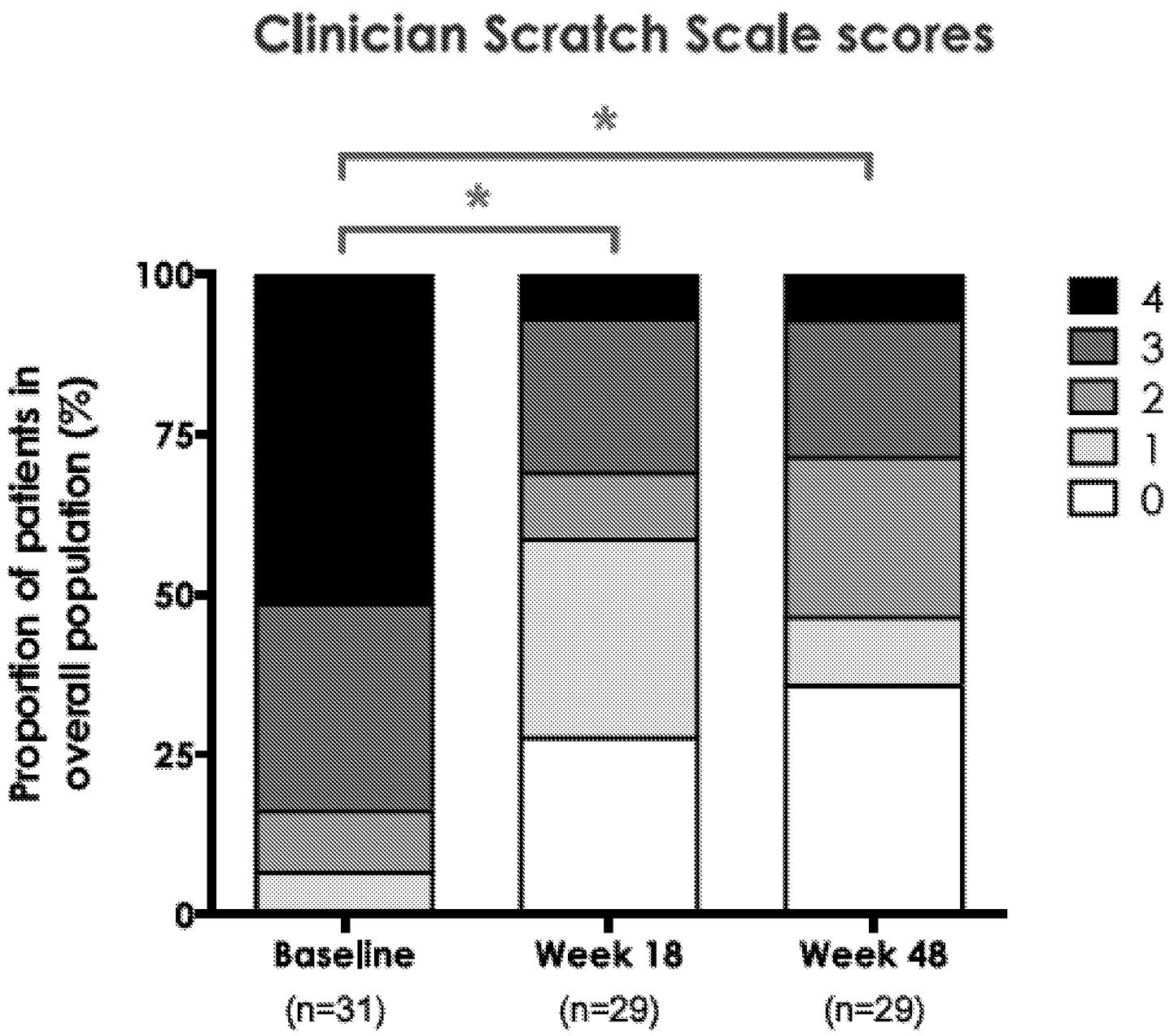
****$p < 0.0001$, change from baseline (overall population)
††$p < 0.01$, ††††$p < 0.0001$ maralixibat versus placebo
Error bars show SEM
LS, least-squares

Fig. 20B



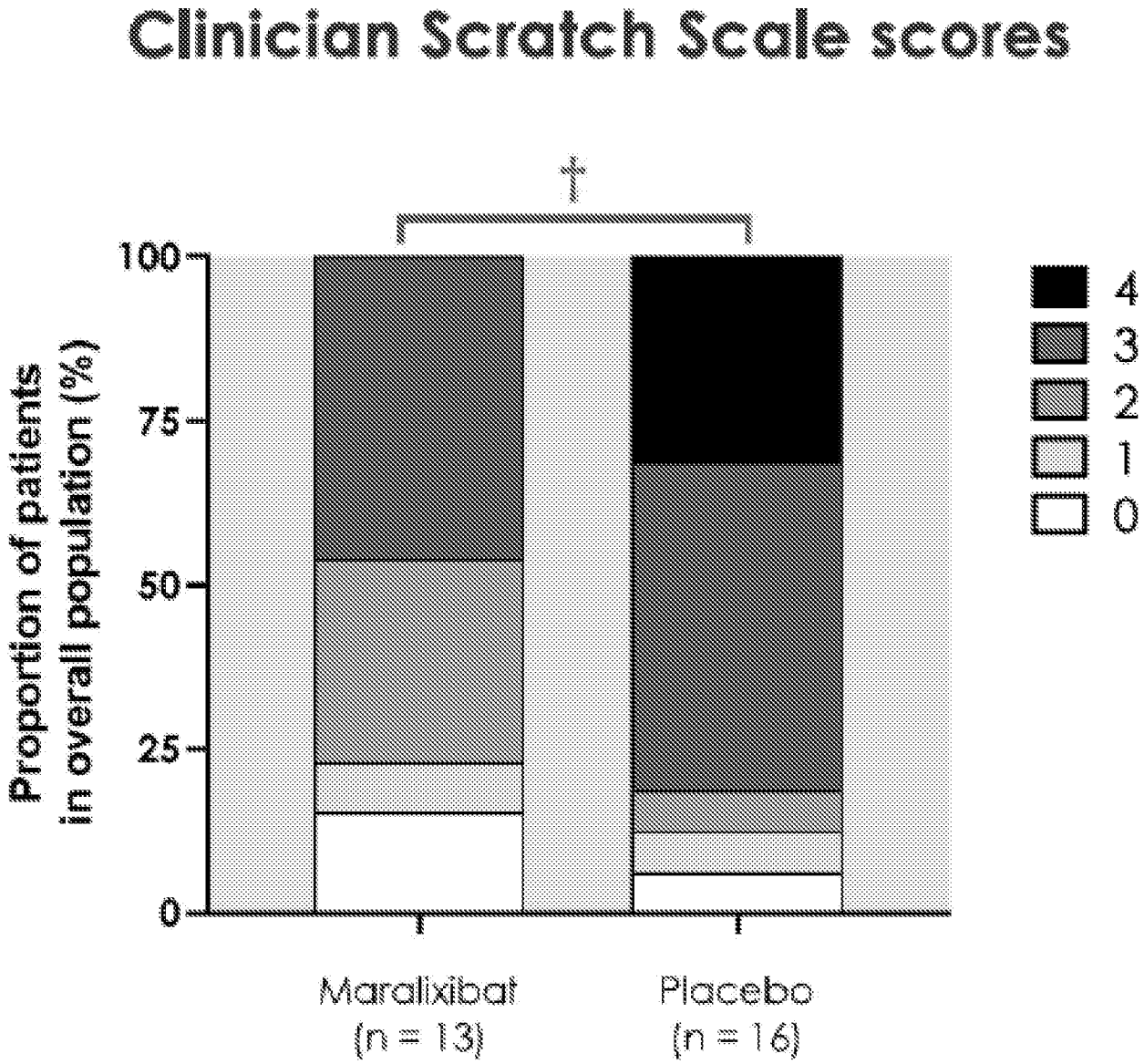
****$p < 0.0001$, change from baseline (overall population)
††$p < 0.01$, ††††$p < 0.0001$ maralixibat versus placebo
Error bars show SEM
LS, least-squares

Fig. 21A



* $p < 0.0001$, change from baseline (overall population)

Fig. 21B



† $p < 0.05$ maralixibat versus placebo (change from week 18)

Fig. 22

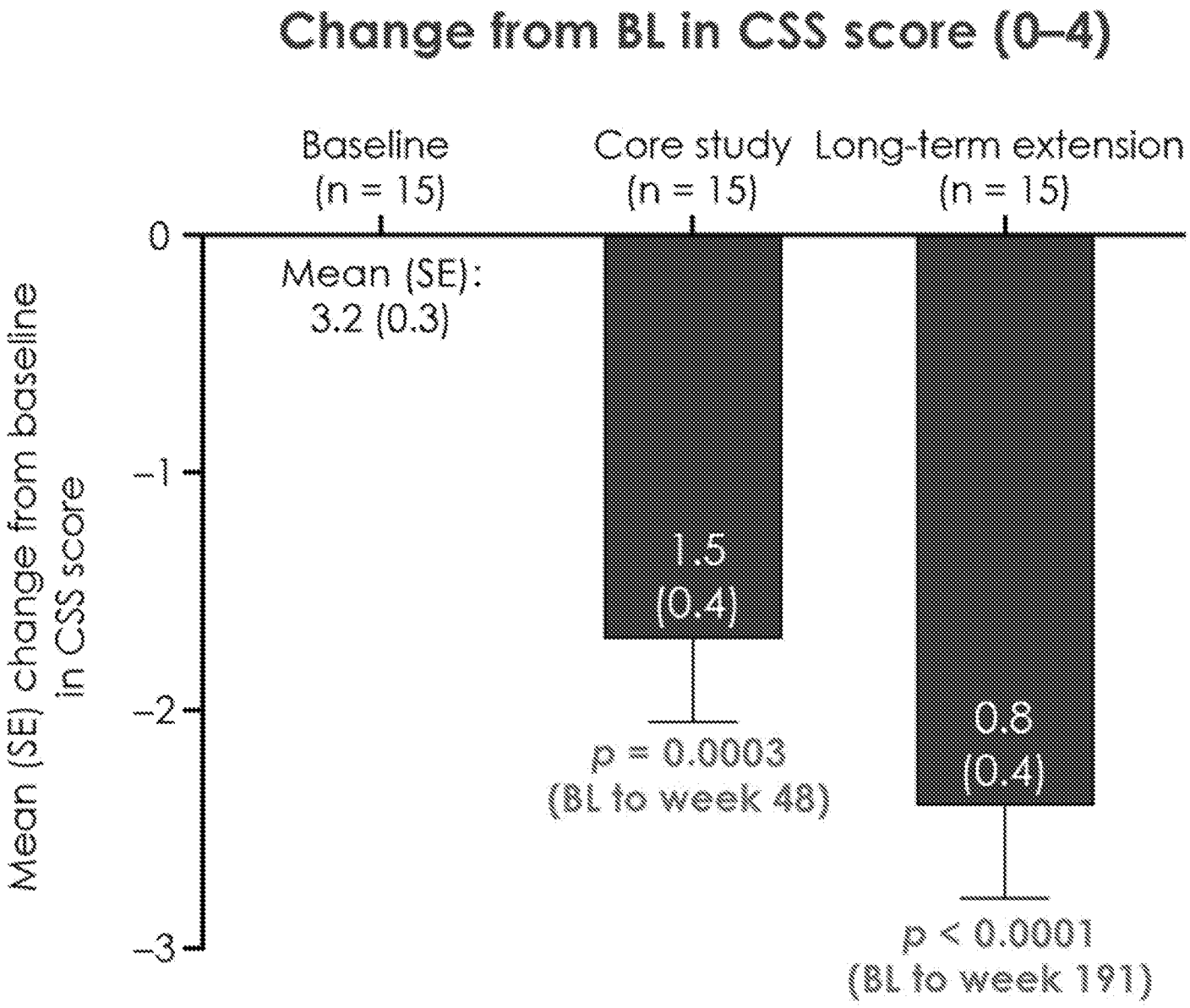

Change from BL in CSS score (0–4)
Baseline
(n = 15)
Core study
(n = 15)
Long-term extension
(n = 15)
Mean (SE):
3.2 (0.3)
1.5
(0.4)
0.8
(0.4)
p = 0.0003
(BL to week 48)
p < 0.0001
(BL to week 191)
Mean (SE) change from baseline in CSS score
0
−1
−2
−3

Fig. 23A

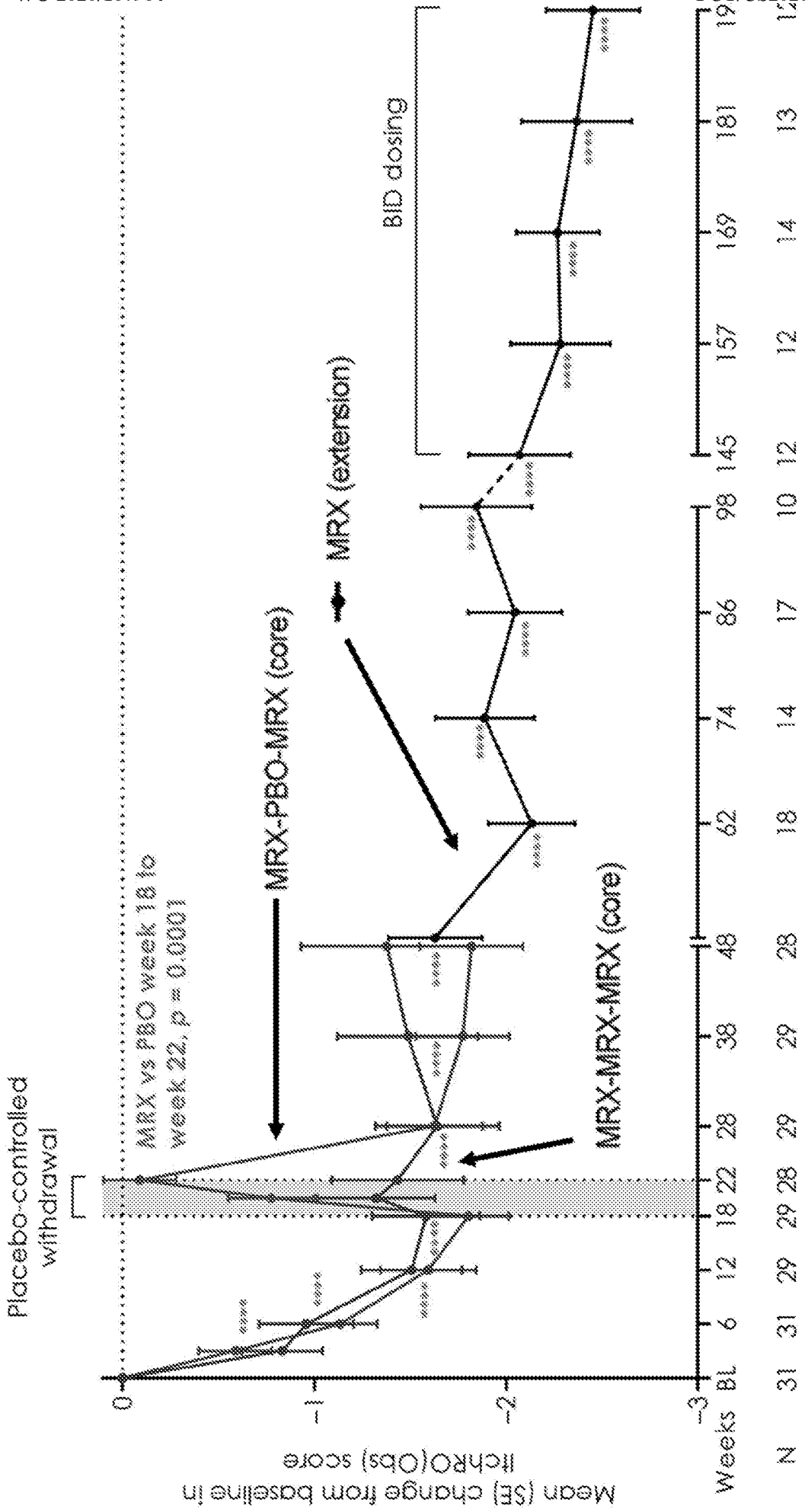

Placebo-controlled withdrawal
MRX vs PBO week 18 to week 22, p = 0.0001
MRX-PBO-MRX (core)
MRX (extension)
MRX-MRX-MRX (core)
BID dosing
Mean (SE) change from baseline in ItchRO(Obs) score
0
−1
−2
−3
Weeks BL 6 12 18 22 28 38 48 62 74 86 98 145 157 169 181 193
N 31 31 29 29 28 29 29 28 18 14 17 10 12 14 13 12
****p ≤ 0.0001, change from baseline (overall population)

Fig. 23B

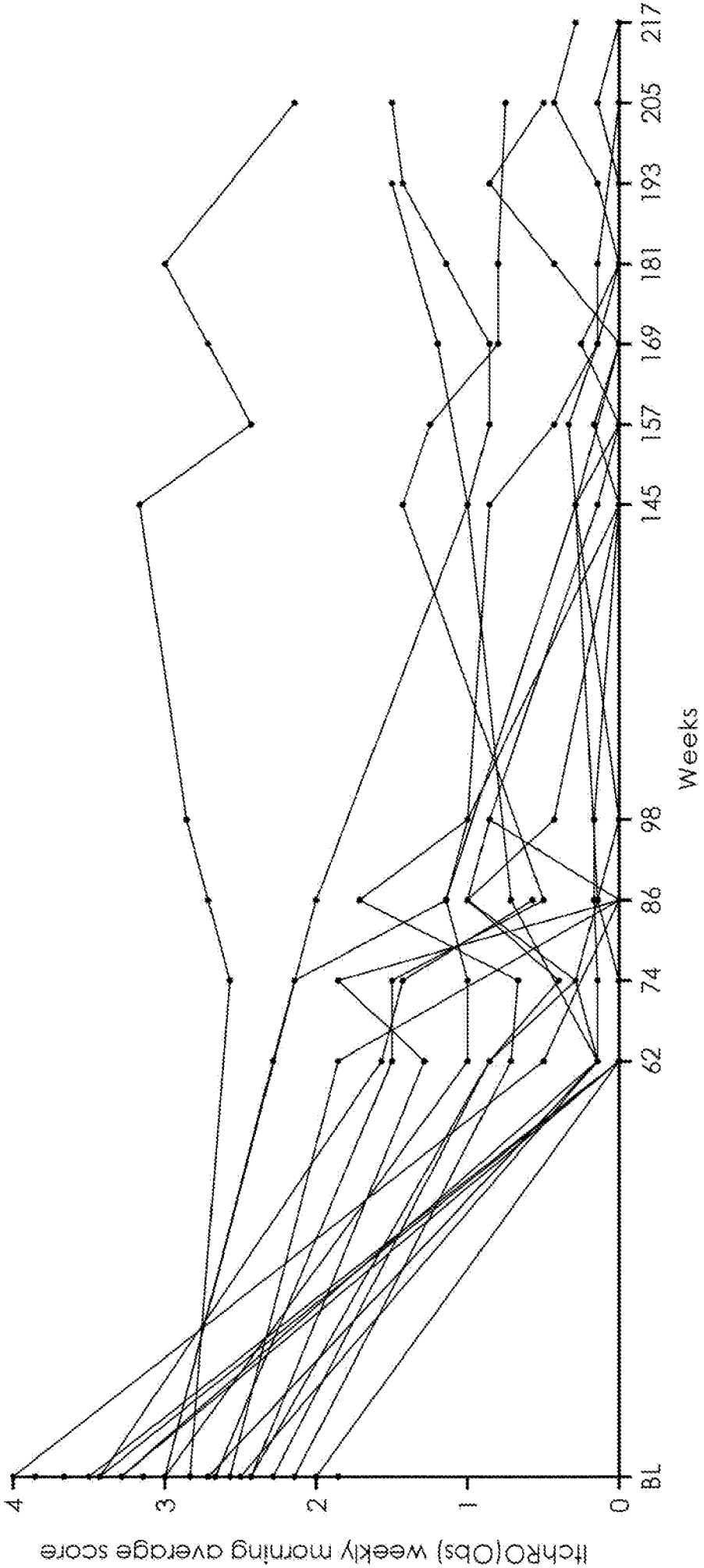

itchRO(Obs) weekly morning average score
0
1
2
3
4
BL
62
74
86
98
145
157
169
181
193
205
217
Weeks

Fig. 23C

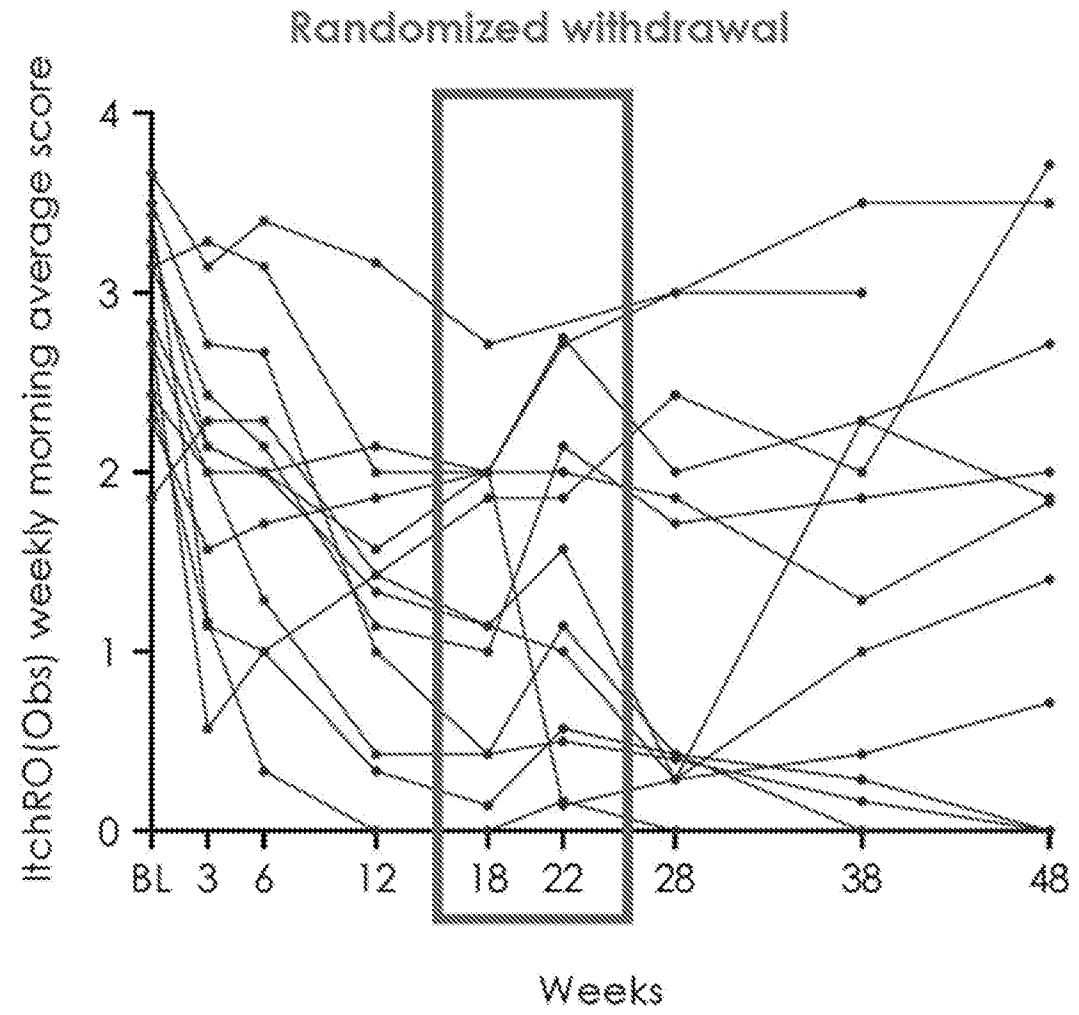

Maralixibat-maralixibat-maralixibat (n = 13)
Randomized withdrawal
ItchRO(Obs) weekly morning average score
0
1
2
3
4
BL
3
6
12
18
22
28
38
48
Weeks

Fig. 23D

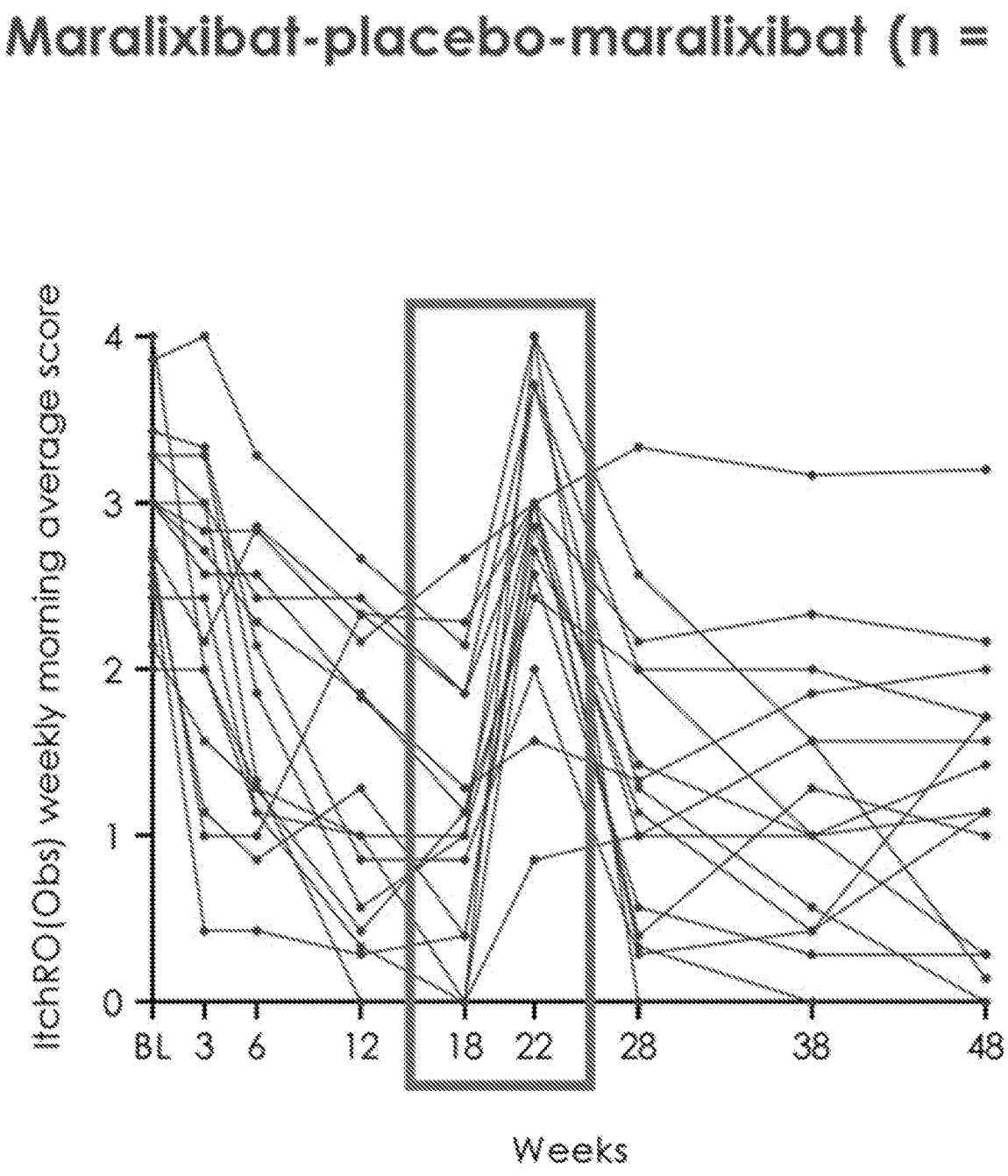
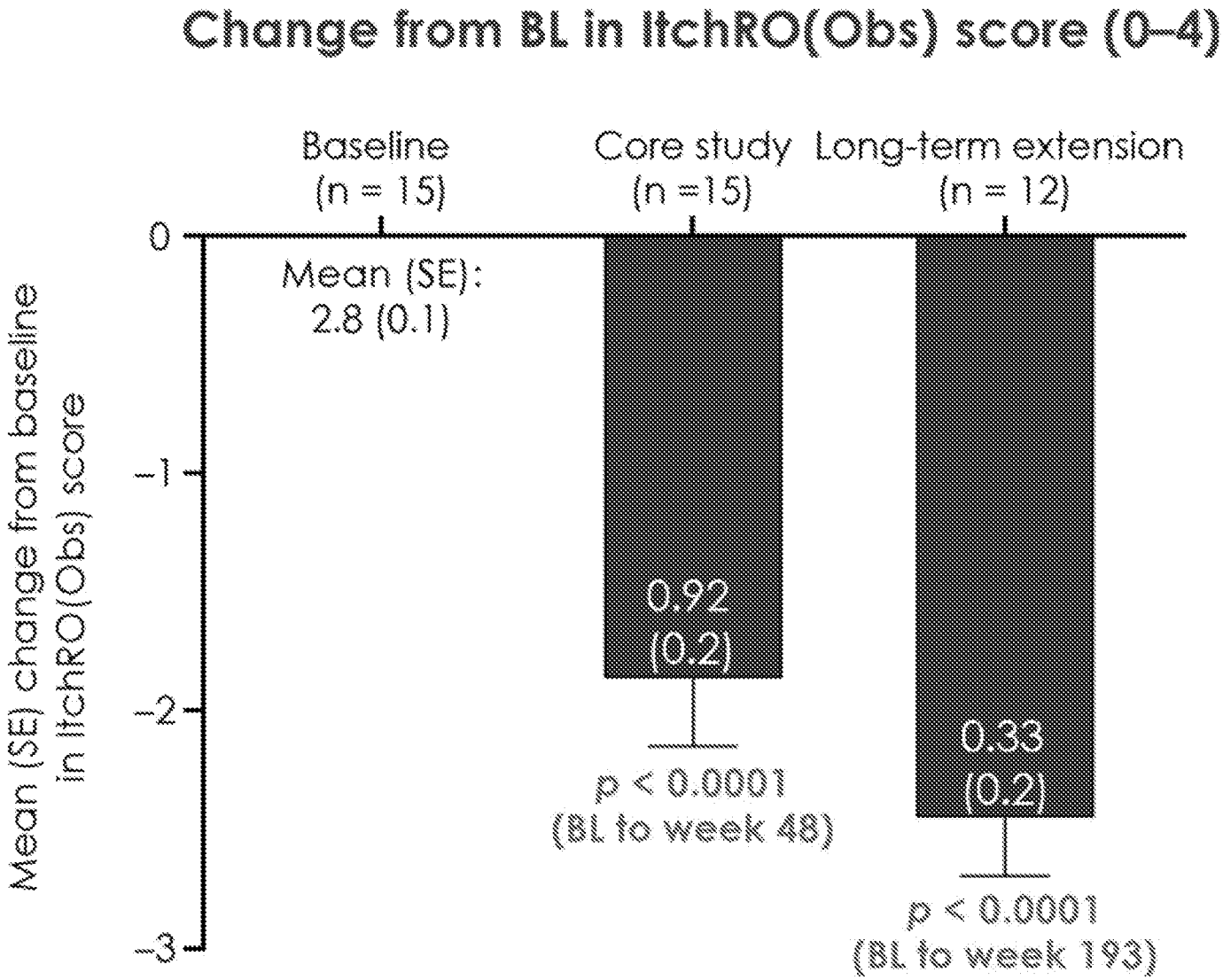

Maralixibat-placebo-maralixibat (n = 16)
ItchRO(Obs) weekly morning average score
0
1
2
3
4
BL
3
6
12
18
22
28
38
48
Weeks

Fig. 24


Change from BL in ItchRO(Obs) score (0–4)
Baseline (n = 15)
Core study (n =15)
Long-term extension (n = 12)
Mean (SE): 2.8 (0.1)
0.92 (0.2)
0.33 (0.2)
p < 0.0001 (BL to week 48)
p < 0.0001 (BL to week 193)
Mean (SE) change from baseline in ItchRO(Obs) score
0
−1
−2
−3

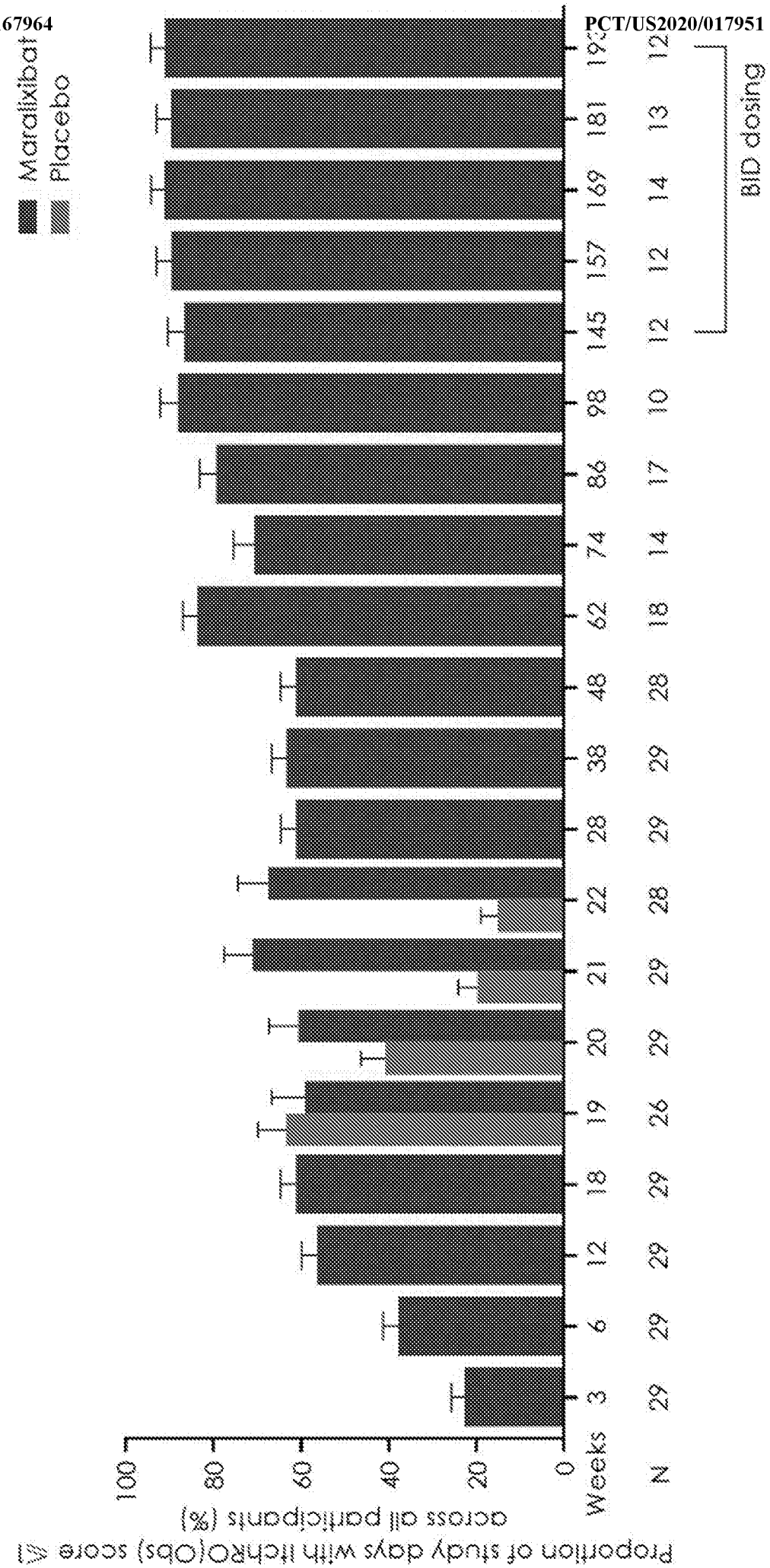
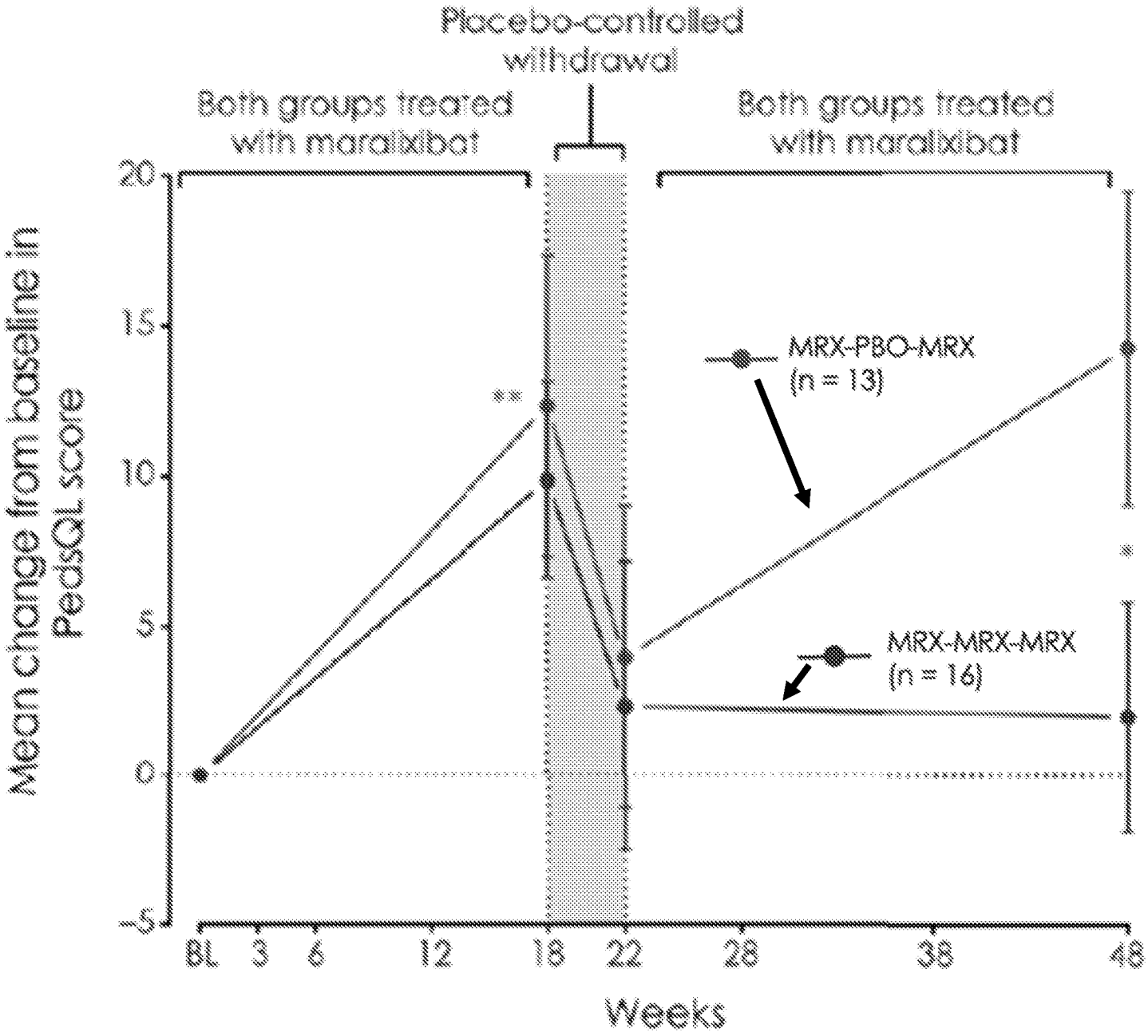

Maralixibat
Placebo
BID dosing
Proportion of study days with itchRO(Obs) score ≤1
across all participants (%)
100
80
60
40
20
0
Weeks
N
3 6 12 18 19 20 21 22 28 38 48 62 74 86 98 145 157 169 181 193
29 29 29 29 26 29 29 28 29 29 28 18 14 17 10 12 12 14 13 12

Fig. 25

Fig. 26



*p < 0.05, **p < 0.01, change from baseline (overall population)

Error bars show standard deviation

Fig. 27

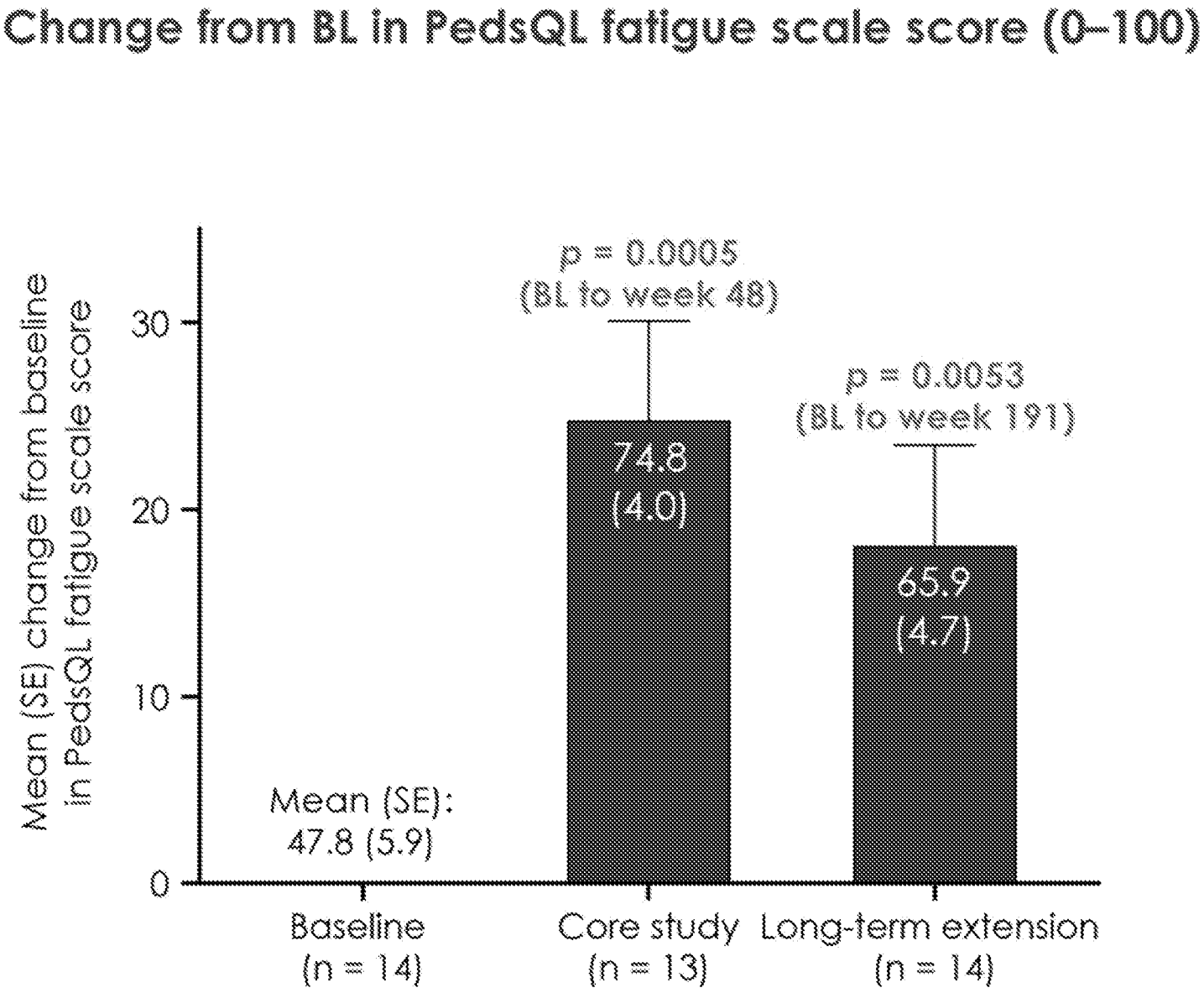
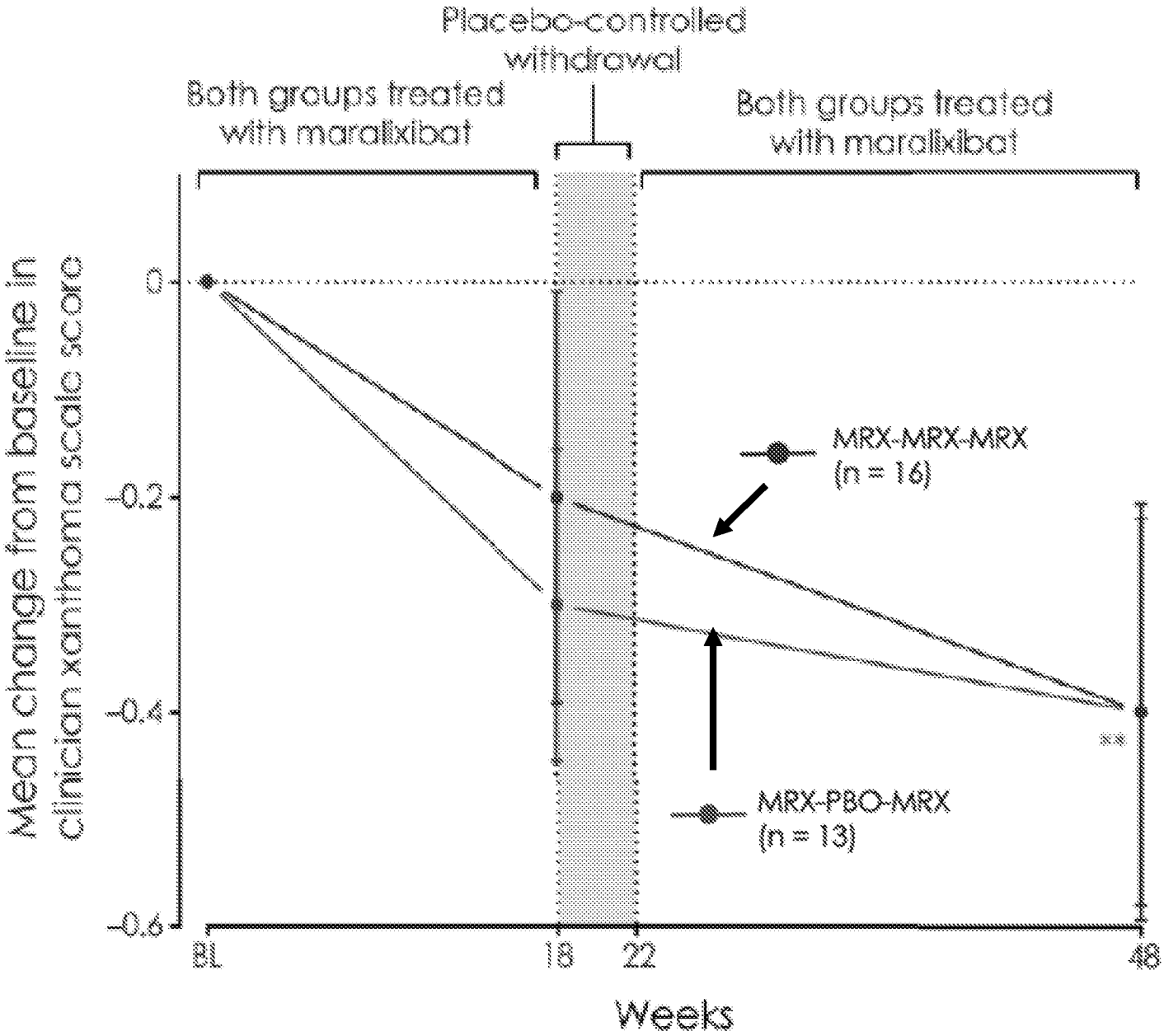

Change from BL in PedsQL fatigue scale score (0–100)
Mean (SE) change from baseline in PedsQL fatigue scale score
30
20
10
0
p = 0.0005
(BL to week 48)
p = 0.0053
(BL to week 191)
74.8
(4.0)
65.9
(4.7)
Mean (SE):
47.8 (5.9)
Baseline
(n = 14)
Core study
(n = 13)
Long-term extension
(n = 14)

Fig. 28



**p < 0.01, change from baseline (overall population)

Error bars show standard deviation

[a] Change from baseline (overall population)

Fig. 29

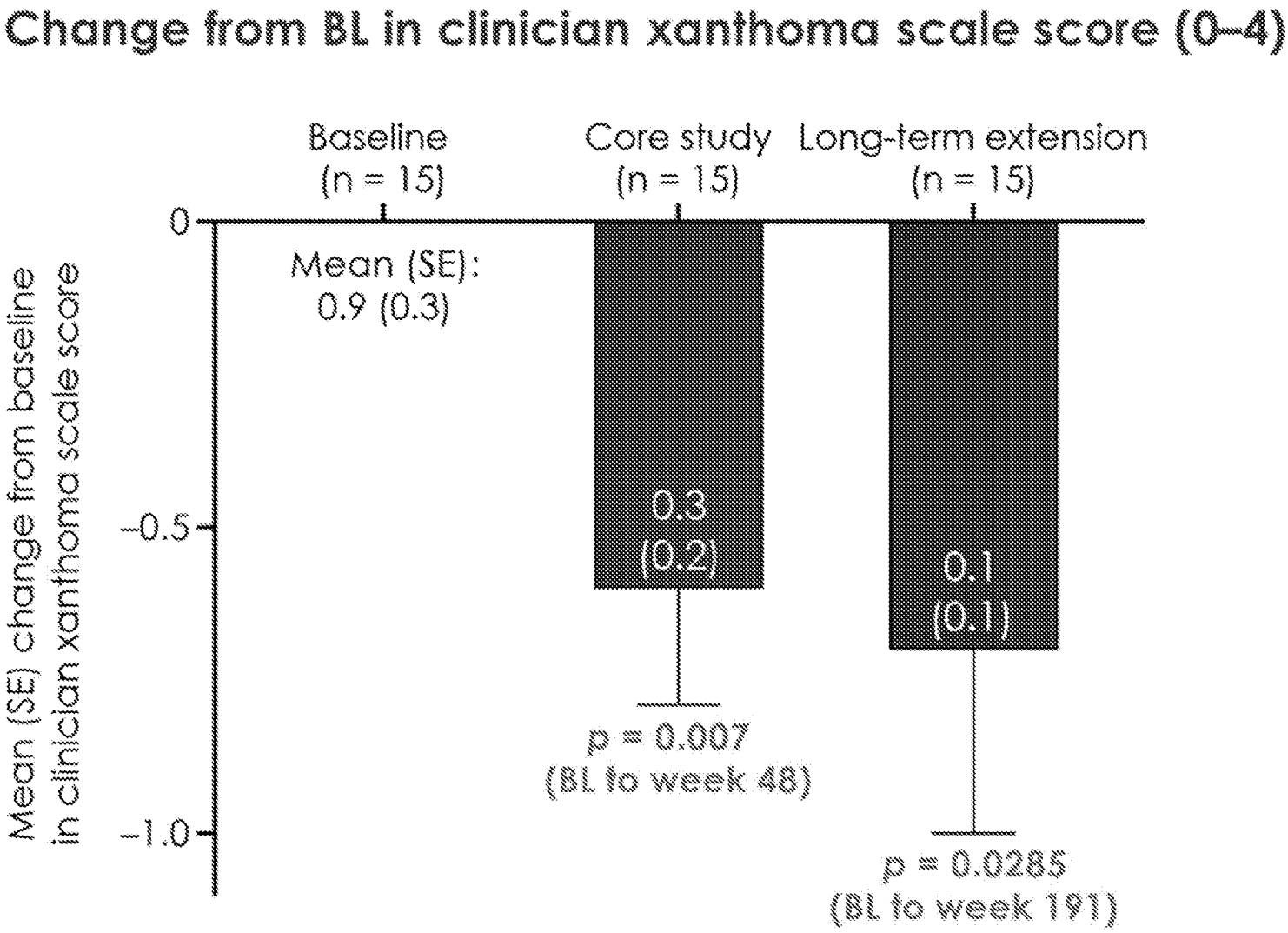
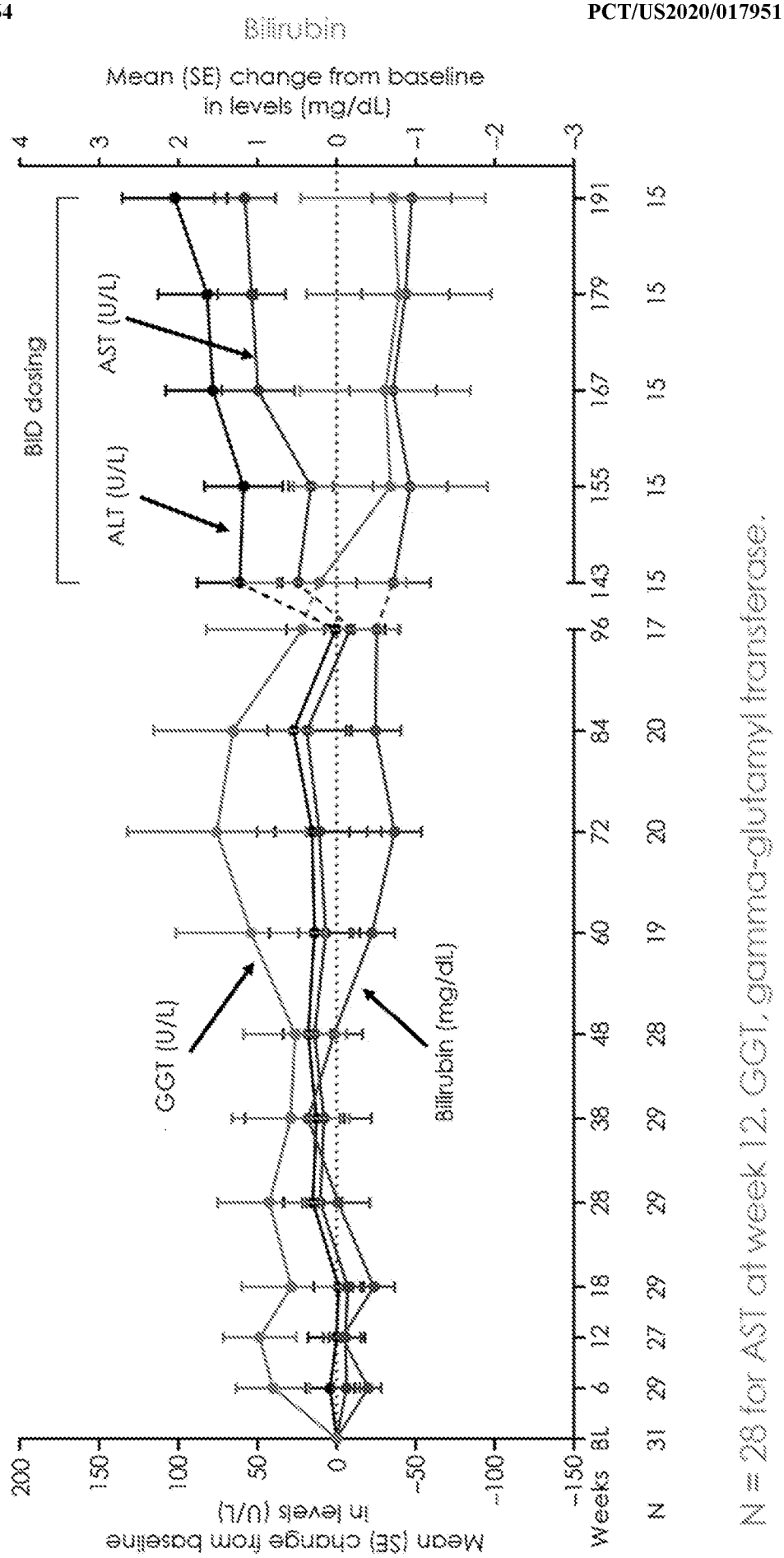

Change from BL in clinician xanthoma scale score (0–4)
Baseline (n = 15)
Core study (n = 15)
Long-term extension (n = 15)
Mean (SE): 0.9 (0.3)
0.3 (0.2)
0.1 (0.1)
p = 0.007 (BL to week 48)
p = 0.0285 (BL to week 191)
Mean (SE) change from baseline in clinician xanthoma scale score
0
−0.5
−1.0

Fig. 30



N = 28 for AST at week 12. GGT, gamma-glutamyl transferase.

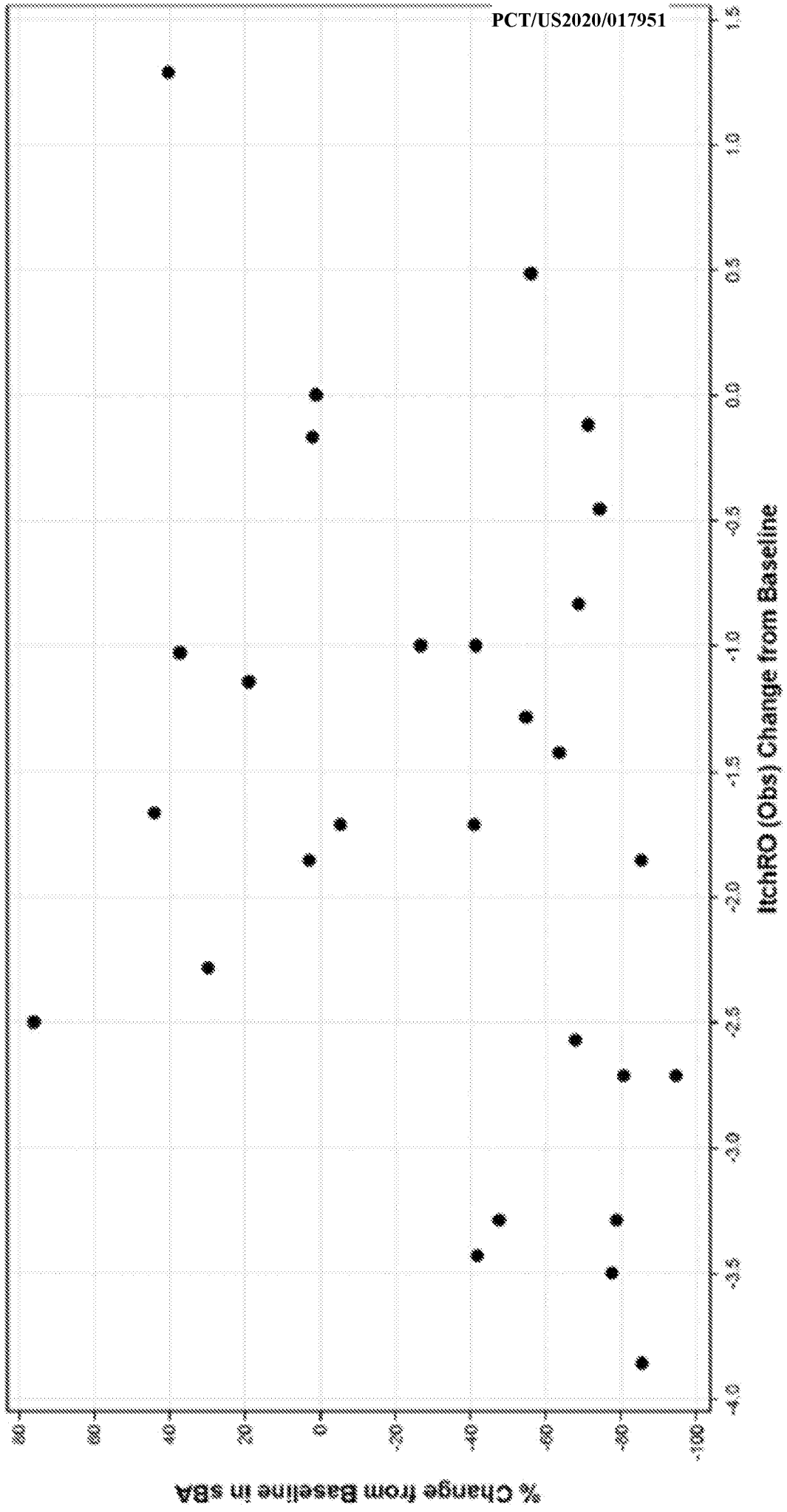

% Change from Baseline in sBA
80
60
40
20
0
-20
-40
-60
-80
-100
ItchRO (Obs) Change from Baseline
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
-4.0

Fig. 31

Fig. 32A

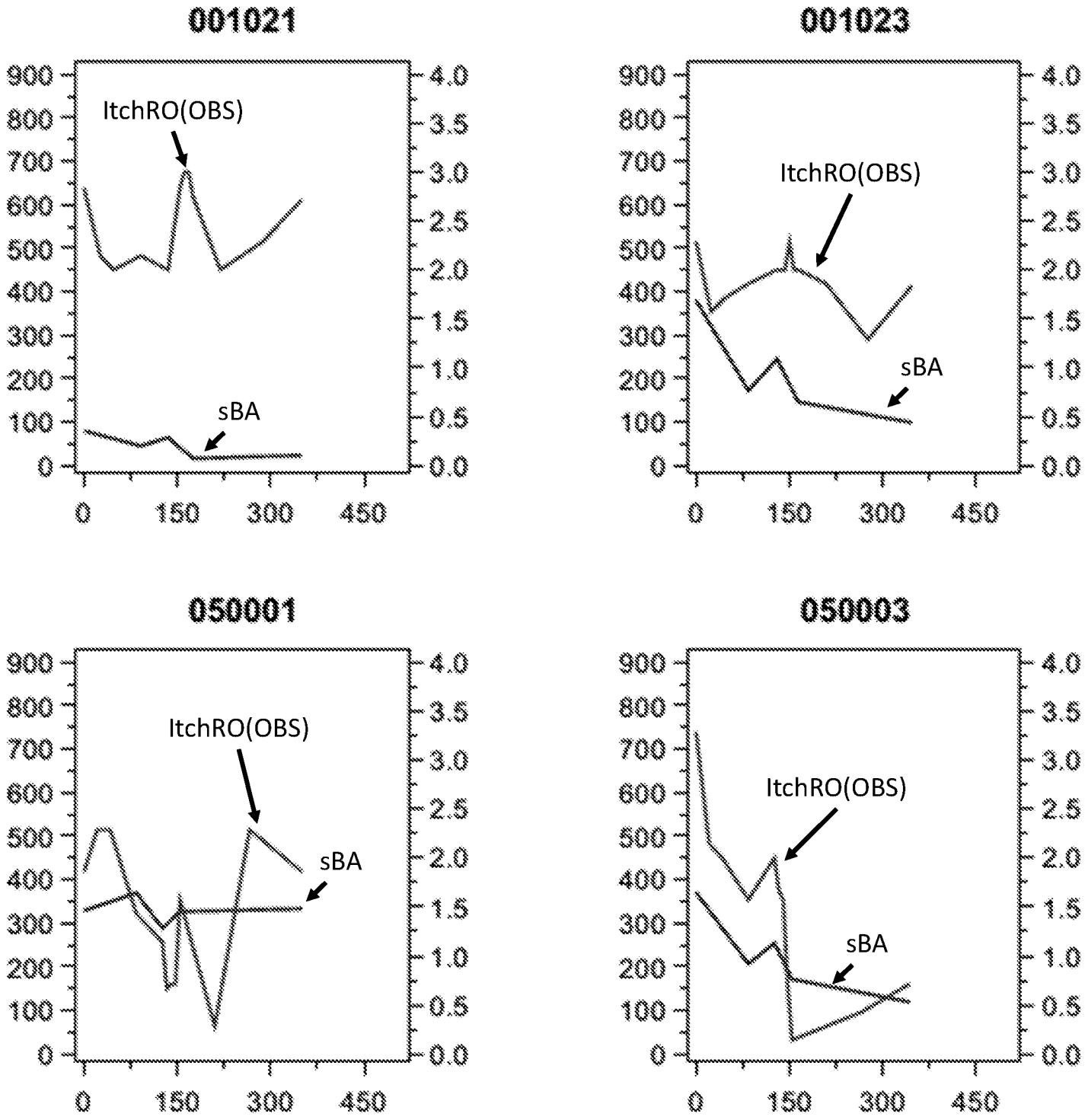

001021
ItchRO(OBS)
sBA
001023
ItchRO(OBS)
sBA
050001
ItchRO(OBS)
sBA
050003
ItchRO(OBS)
sBA
0
100
200
300
400
500
600
700
800
900
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
0
150
300
450

Fig. 32B

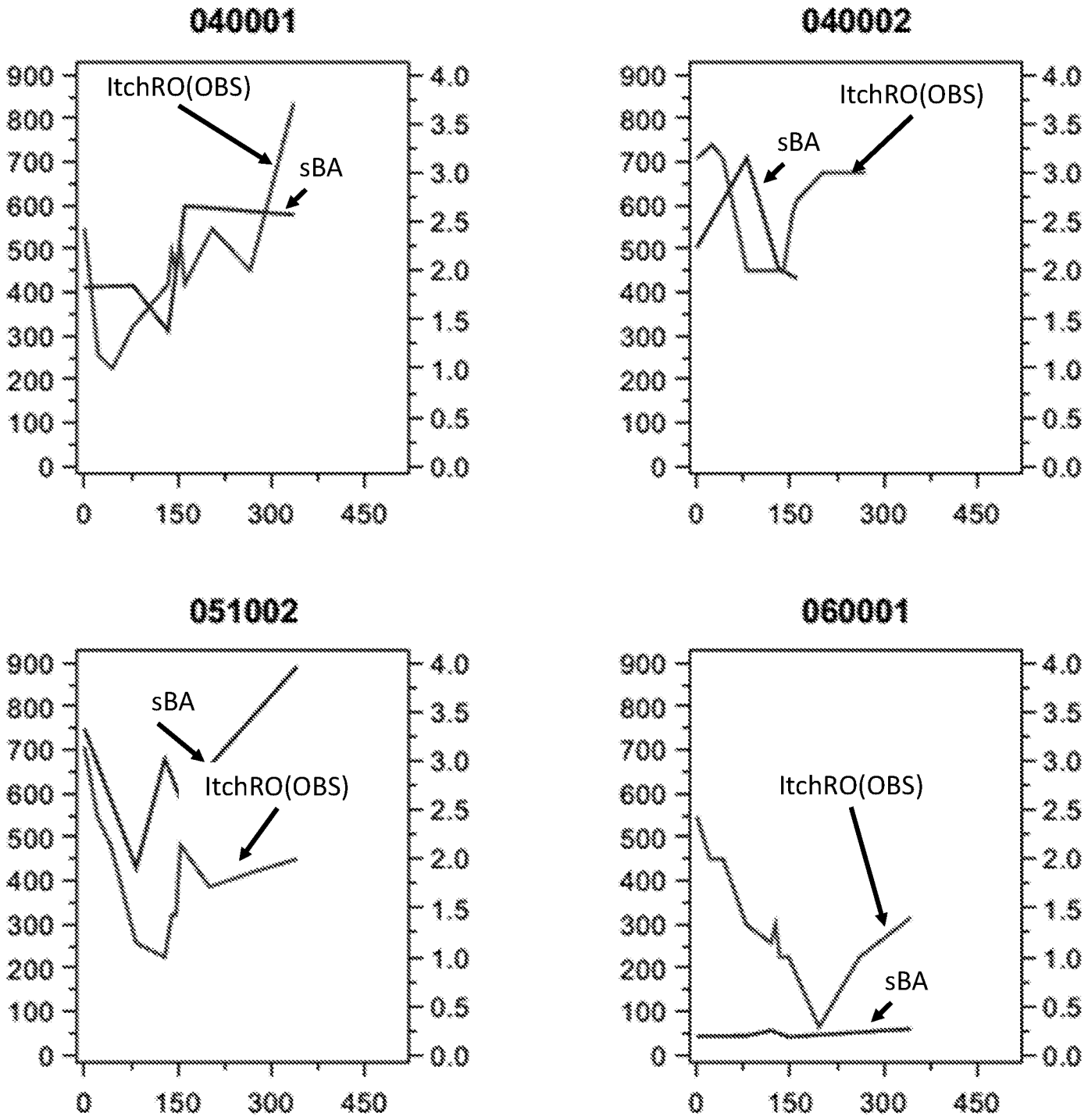

040001
ItchRO(OBS)
sBA
040002
ItchRO(OBS)
sBA
051002
sBA
ItchRO(OBS)
060001
ItchRO(OBS)
sBA
0
100
200
300
400
500
600
700
800
900
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
0
150
300
450

Fig. 32C

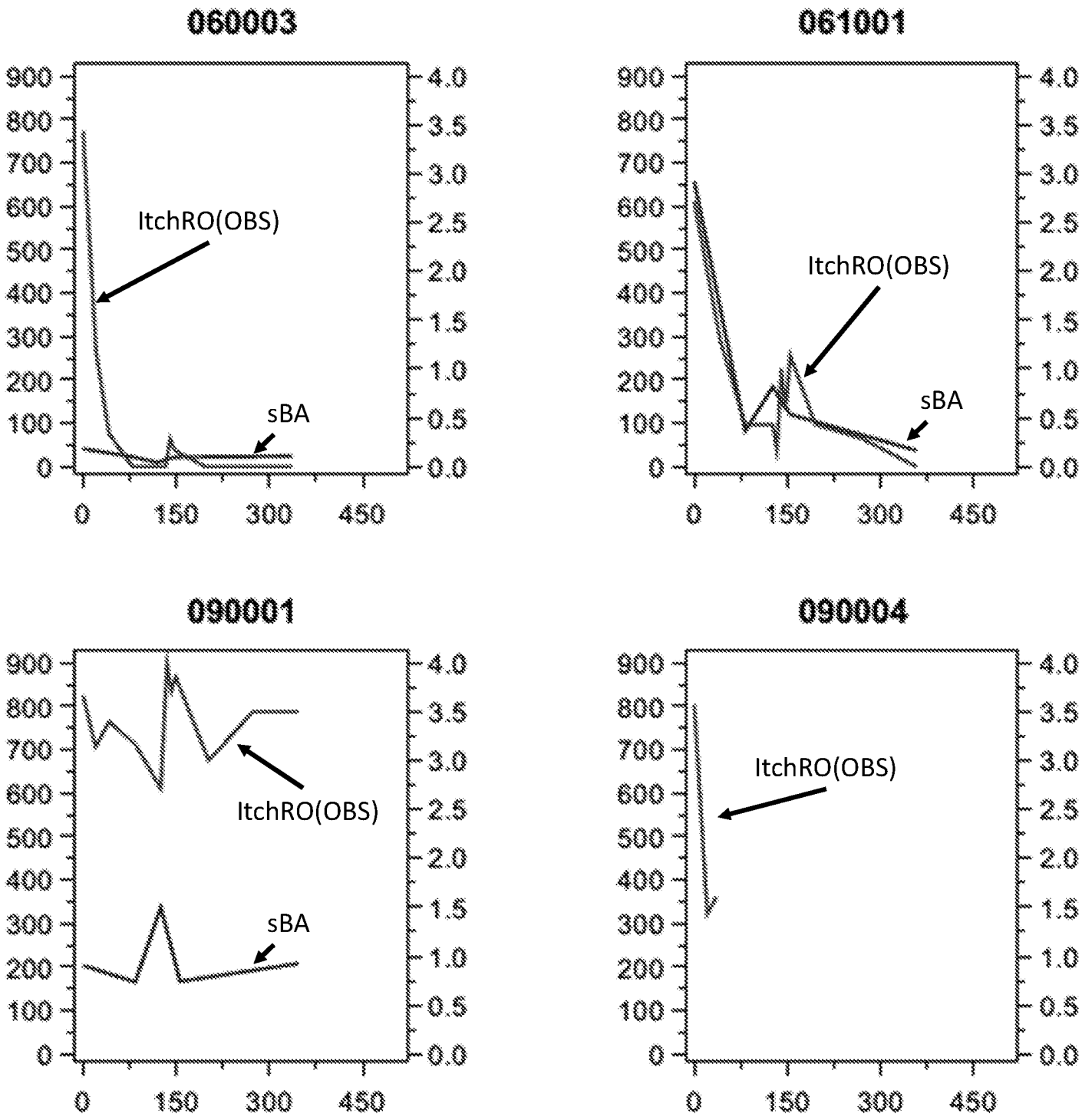

060003
ItchRO(OBS)
sBA
061001
ItchRO(OBS)
sBA
090001
ItchRO(OBS)
sBA
090004
ItchRO(OBS)
0
100
200
300
400
500
600
700
800
900
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
0
150
300
450

Fig. 32D

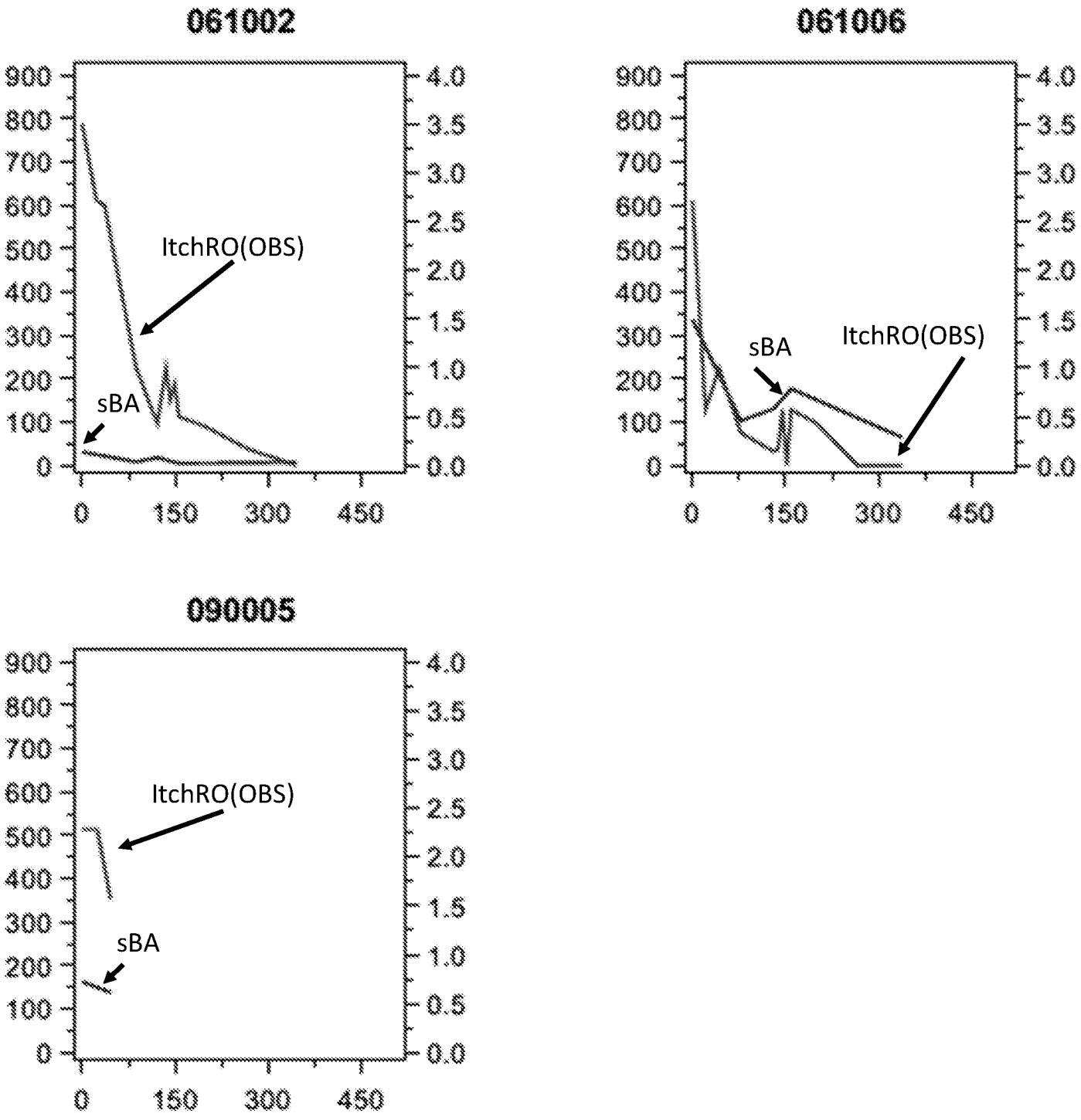

061002
ItchRO(OBS)
sBA
061006
sBA
ItchRO(OBS)
090005
ItchRO(OBS)
sBA
900
800
700
600
500
400
300
200
100
0
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
150
300
450

Fig. 32E

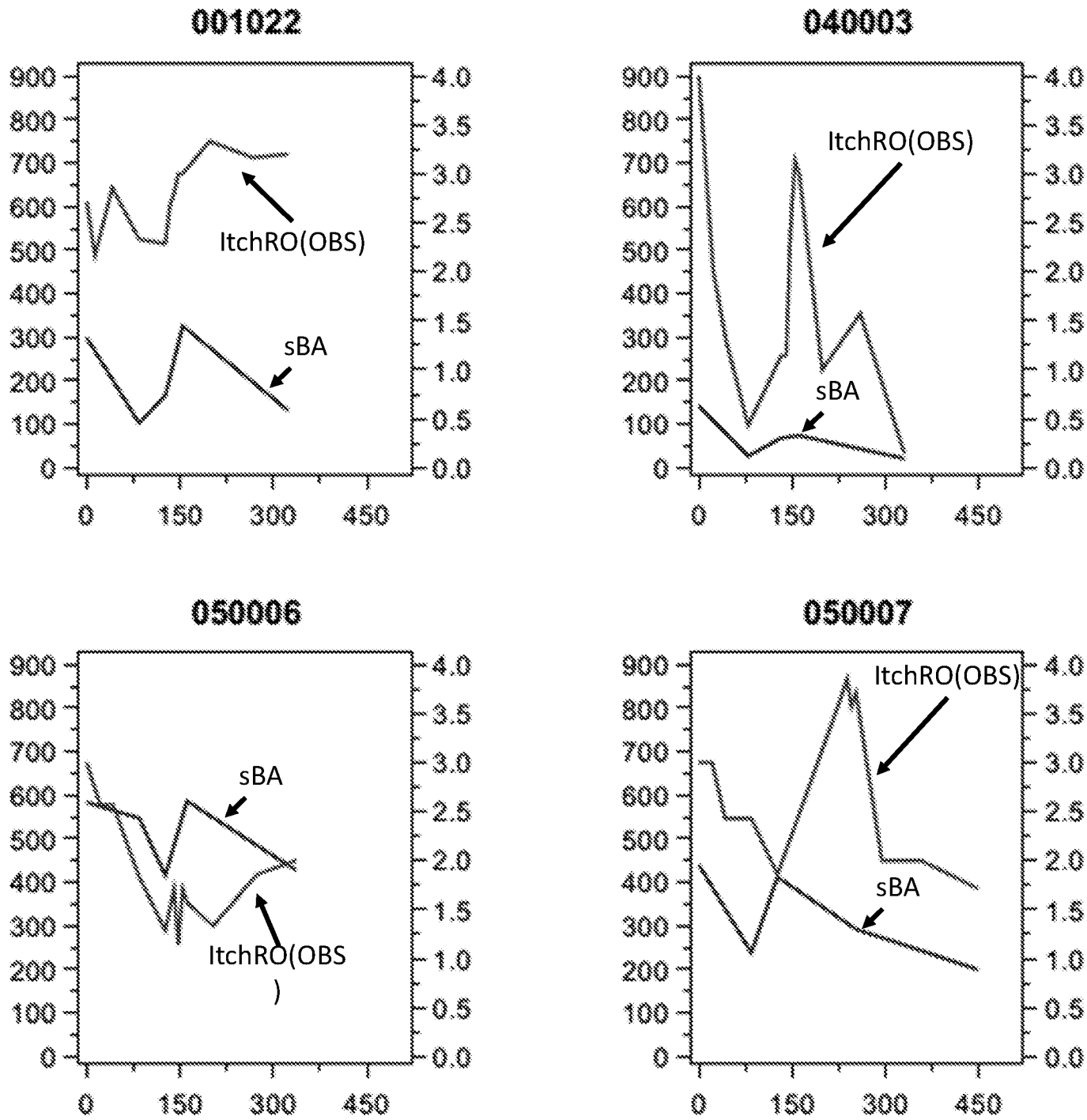

001022
ItchRO(OBS)
sBA
040003
ItchRO(OBS)
sBA
050006
sBA
ItchRO(OBS)
050007
ItchRO(OBS)
sBA
0
150
300
450
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
100
200
300
400
500
600
700
800
900

Fig. 32F

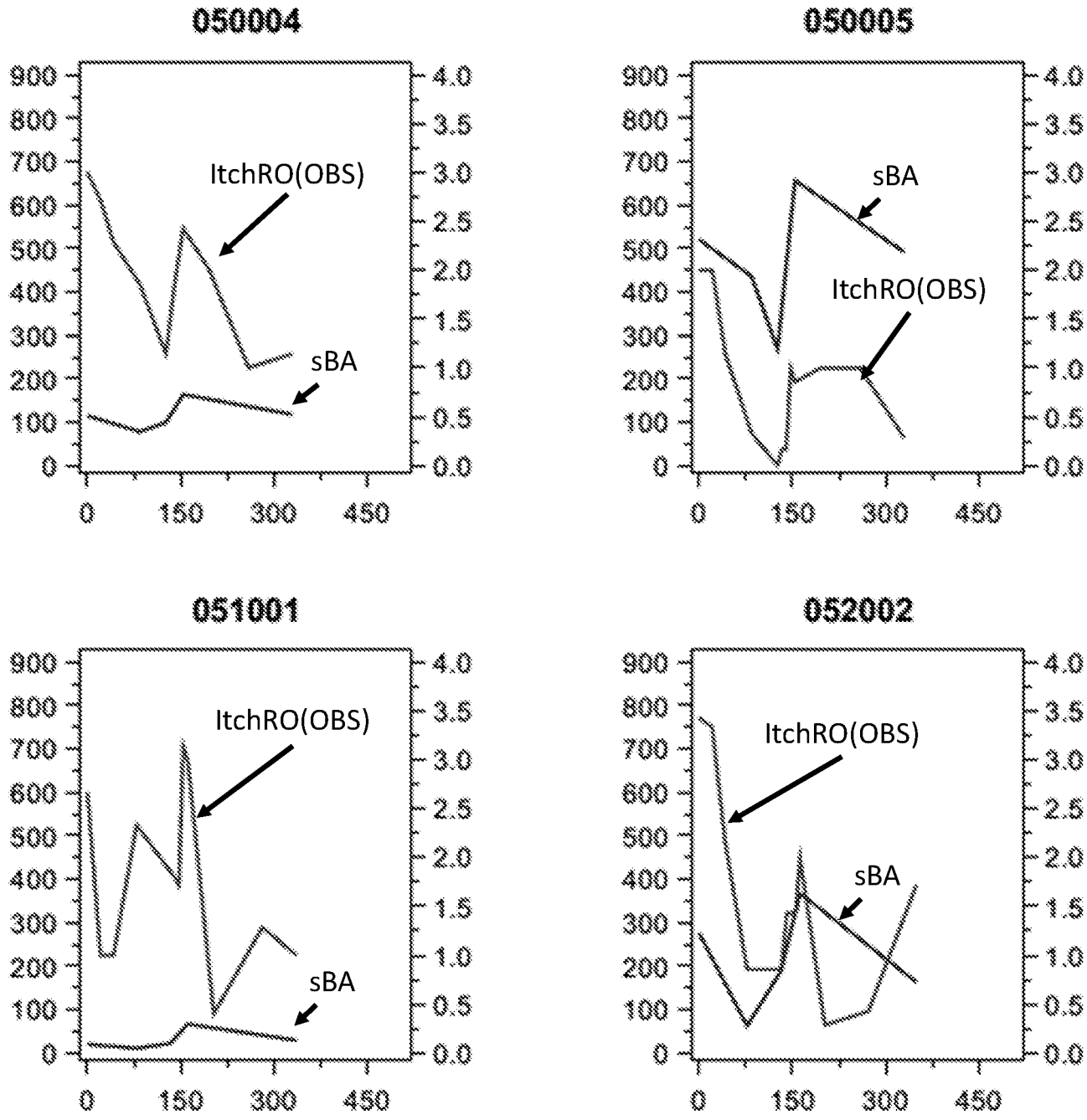

050004
ItchRO(OBS)
sBA
050005
sBA
ItchRO(OBS)
051001
ItchRO(OBS)
sBA
052002
ItchRO(OBS)
sBA
0
100
200
300
400
500
600
700
800
900
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
0
150
300
450

Fig. 32G

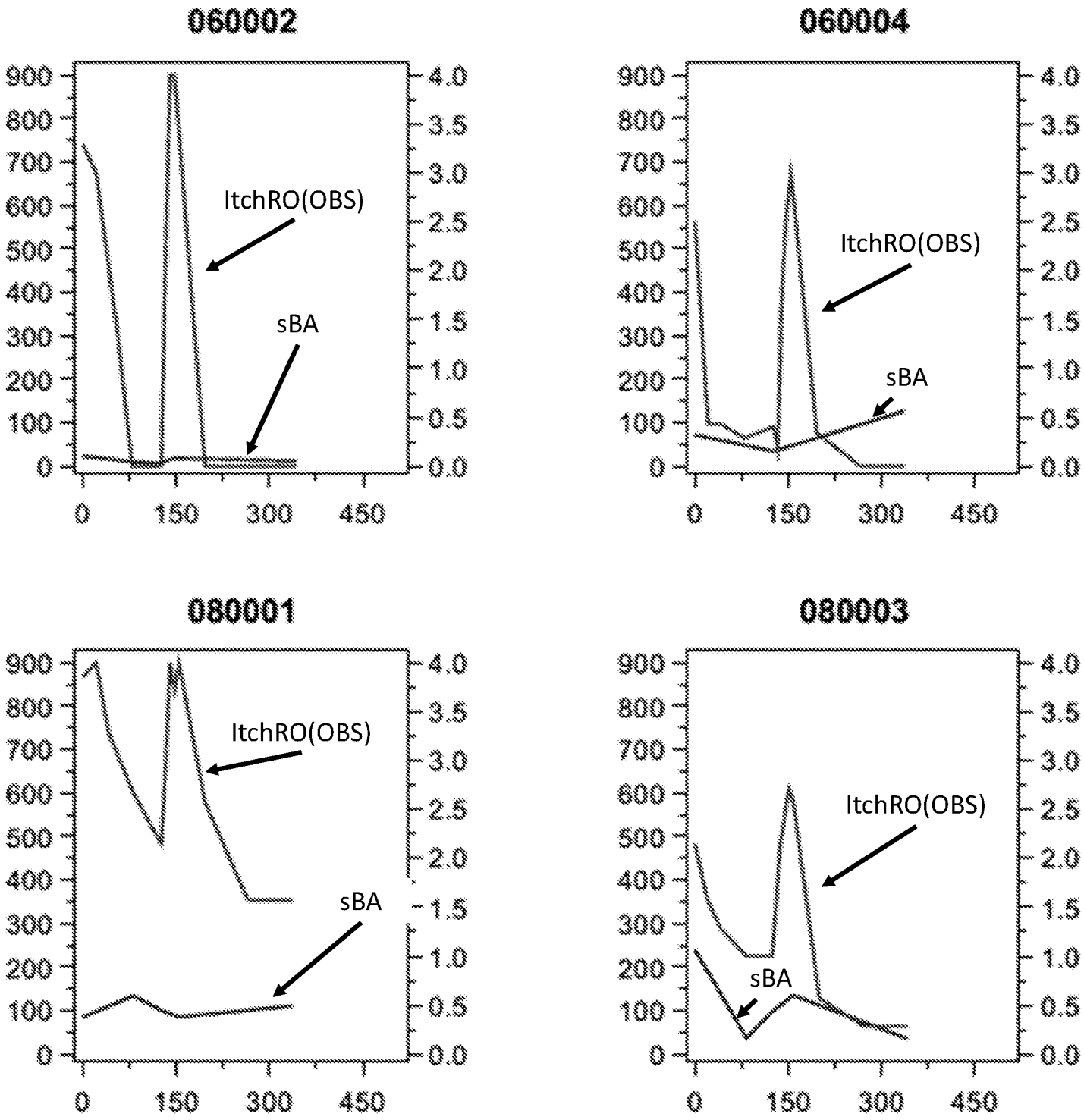

060002
ItchRO(OBS)
sBA
060004
ItchRO(OBS)
sBA
080001
ItchRO(OBS)
sBA
080003
ItchRO(OBS)
sBA
0
100
200
300
400
500
600
700
800
900
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
0
150
300
450

Fig. 32H

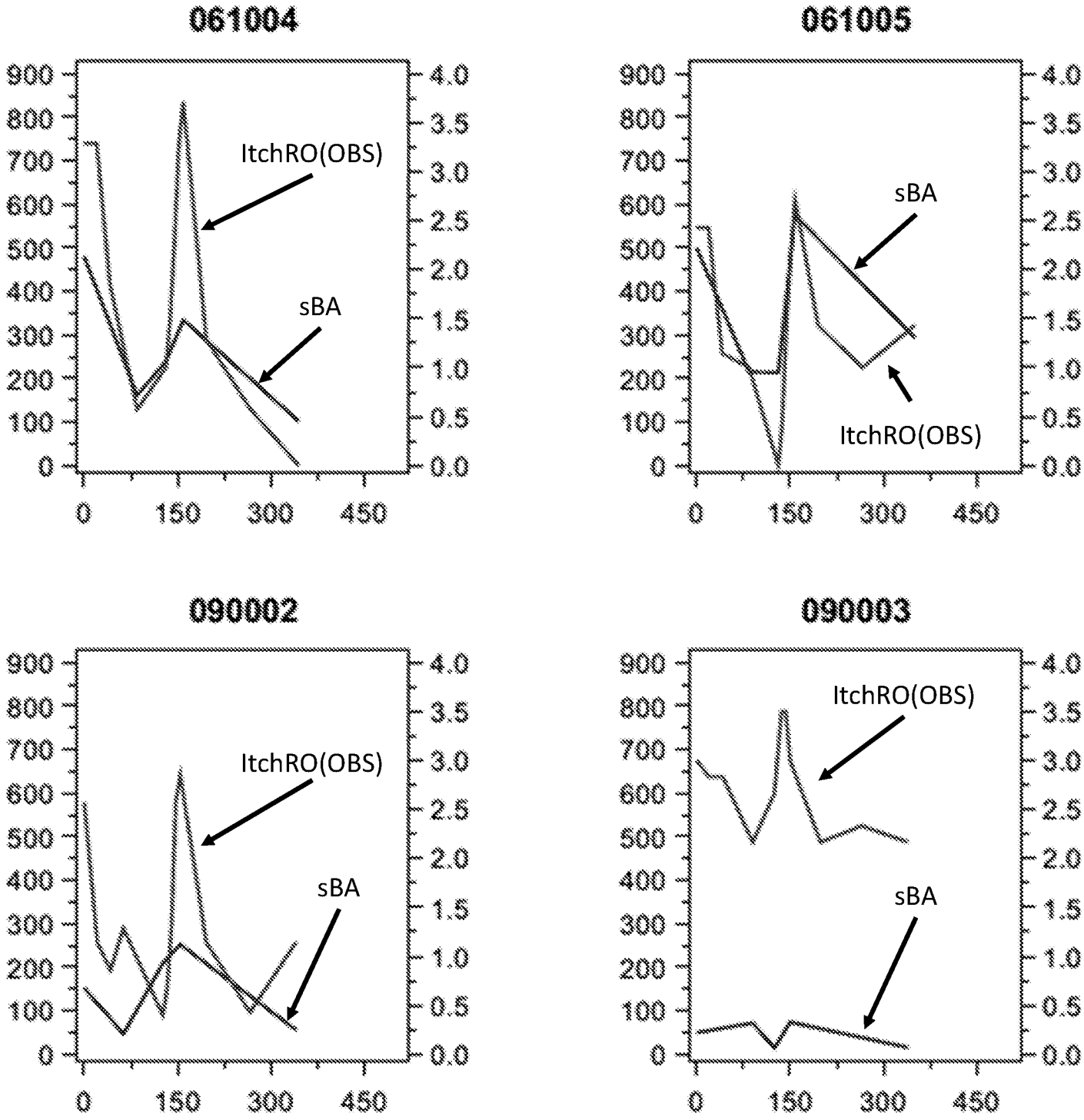

061004
ItchRO(OBS)
sBA
061005
sBA
ItchRO(OBS)
090002
ItchRO(OBS)
sBA
090003
ItchRO(OBS)
sBA
0
100
200
300
400
500
600
700
800
900
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
0
150
300
450

Fig. 33

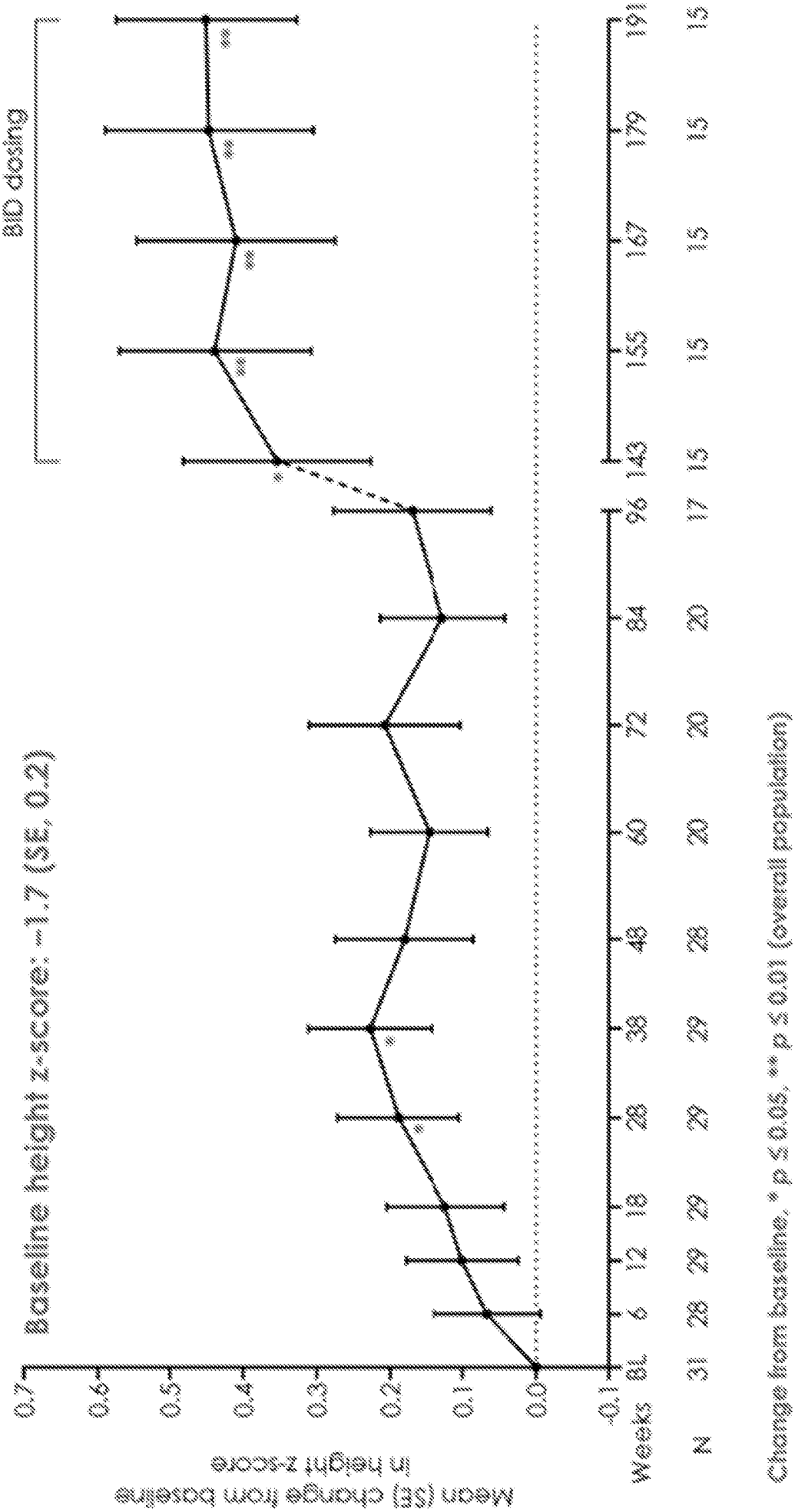
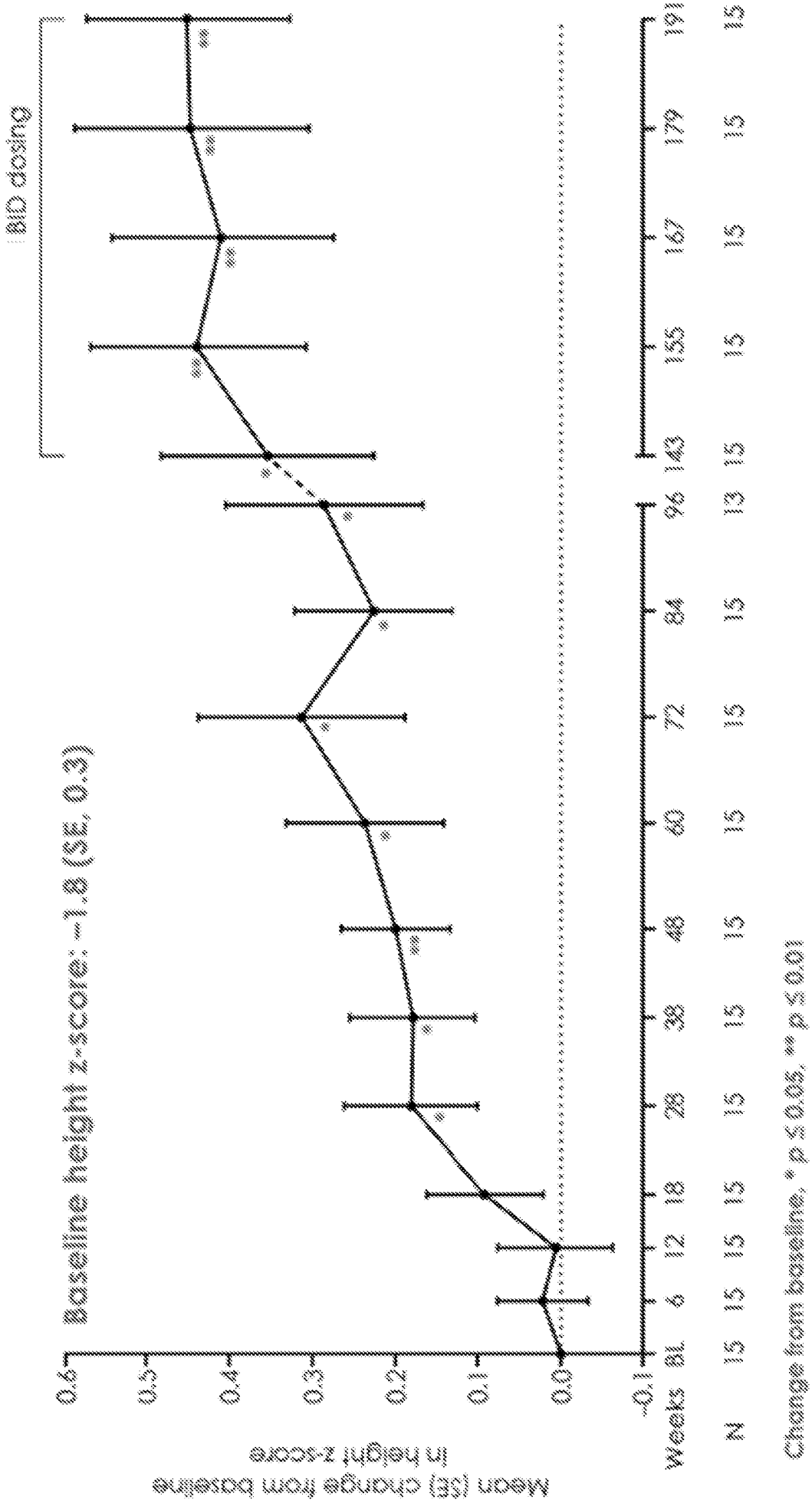

Mean (SE) change from baseline in height z-score
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
Baseline height z-score: -1.7 (SE, 0.2)
BID dosing
Weeks
BL 6 12 18 28 38 48 60 72 84 96 143 155 167 179 191
N
31 28 29 29 29 29 28 29 28 20 20 20 17 15 15 15 15
Change from baseline, * p ≤ 0.05, ** p ≤ 0.01 (overall population)

Fig. 34


Mean (SE) change from baseline in height z-score
Baseline height z-score: -1.8 (SE, 0.3)
BID dosing
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
Weeks BL 6 12 18 28 38 48 60 72 84 96 143 155 167 179 191
N 15 15 15 15 15 15 15 15 15 13 15 15 15 15 15
Change from baseline, * p ≤ 0.05, ** p ≤ 0.01

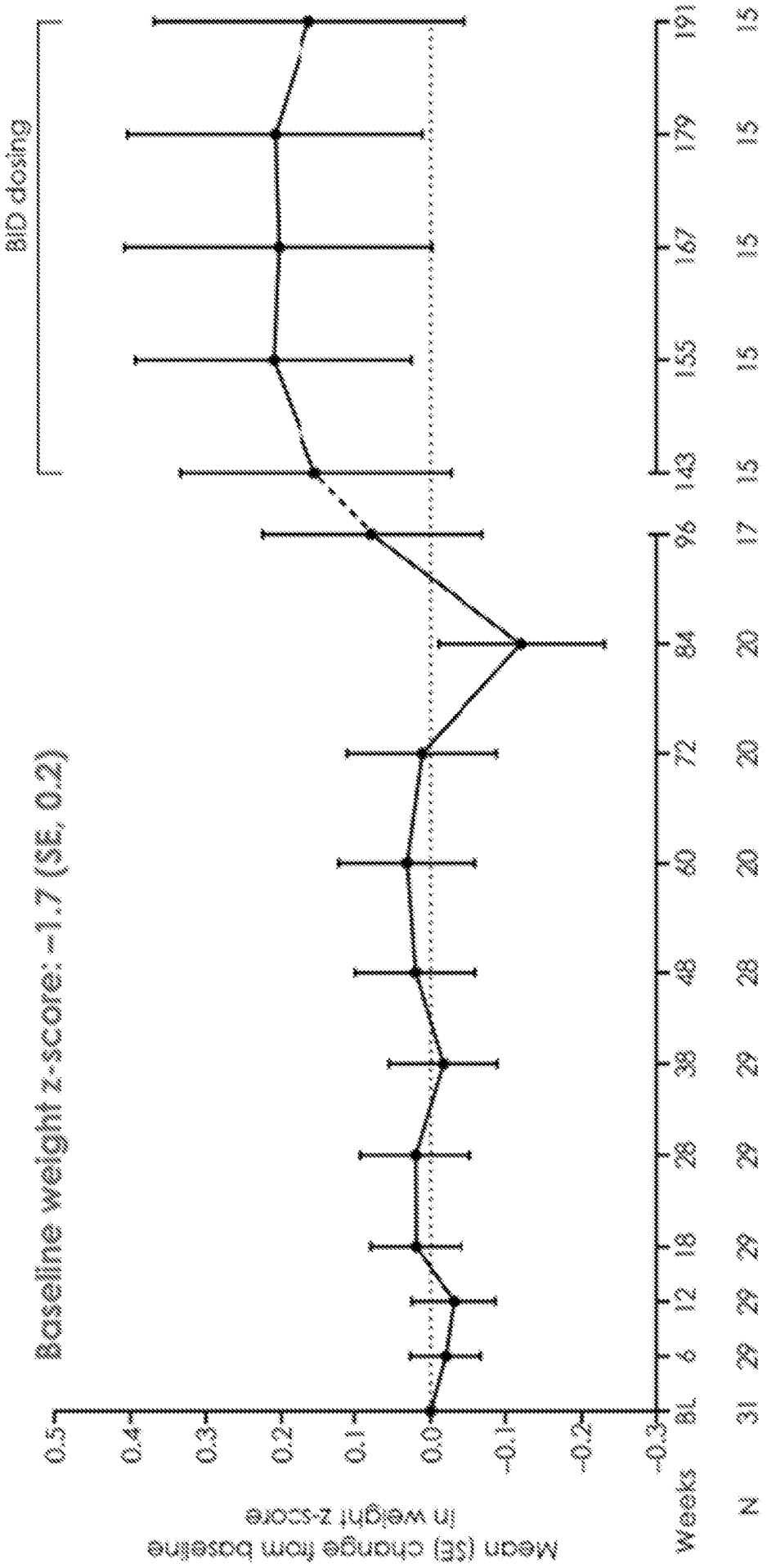

Mean (SE) change from baseline in weight z-score
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2
-0.3
Baseline weight z-score: -1.7 (SE, 0.2)
BID dosing
Weeks
N
BL 6 12 18 26 38 48 60 72 84 96 140 155 167 179 191
31 29 29 28 28 29 28 20 20 20 17 15 15 15 15

Fig. 35

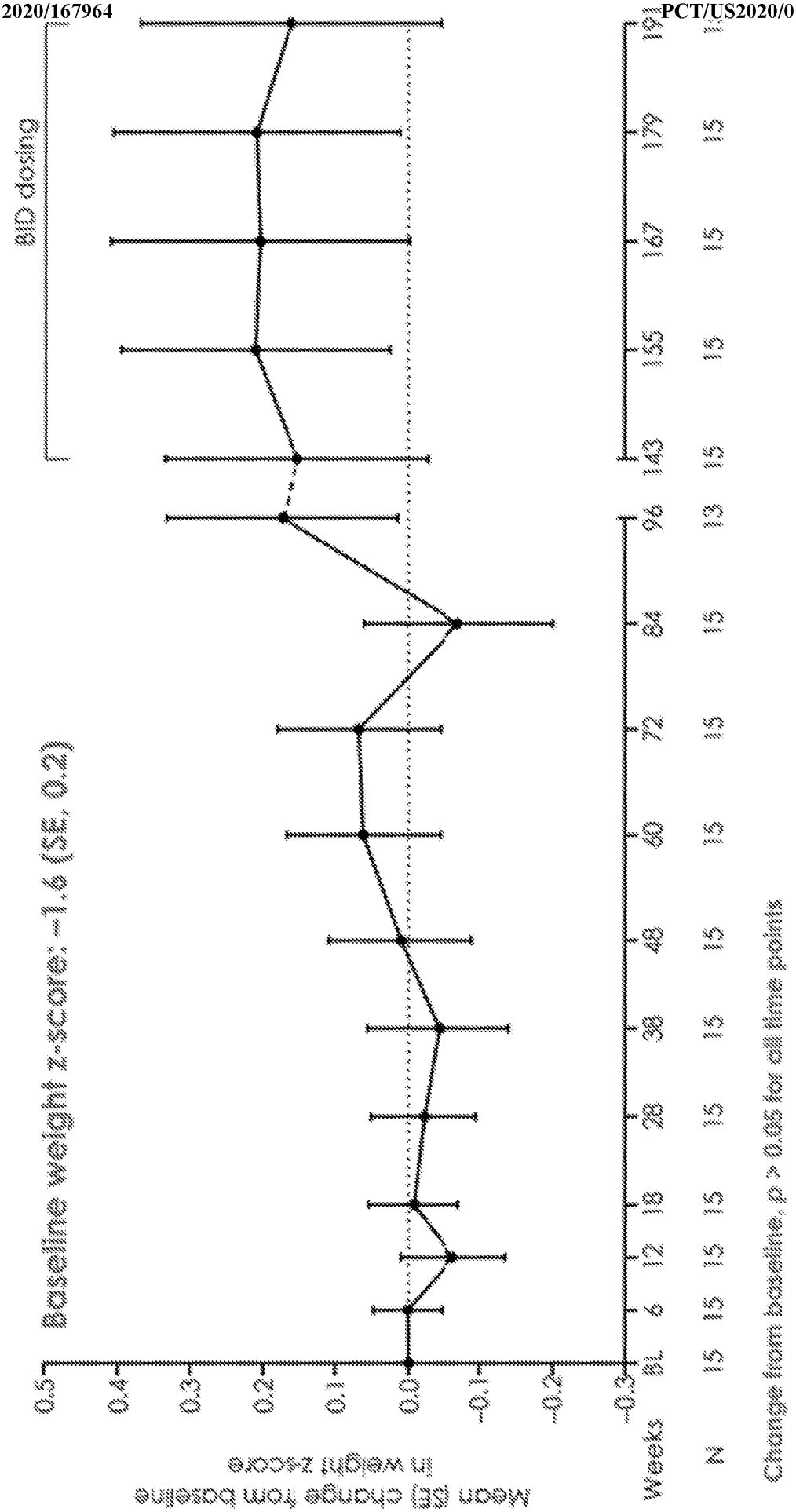

BID dosing
Baseline weight z-score: −1.6 (SE, 0.2)
Mean (SE) change from baseline in weight z-score
0.5
0.4
0.3
0.2
0.1
0.0
−0.1
−0.2
−0.3
Weeks
BL 6 12 18 28 38 48 60 72 84 96 143 155 167 179 191
N
15 15 15 15 15 15 15 15 15 13 15 15 15 15
Change from baseline, p > 0.05 for all time points

Fig. 36

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 20/17951

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/4995; A61P 1/16 (2020.01)

CPC - C07D 295/13; C12Q 1/6883; A61P 1/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2014/0243281 A1 (LUMENA PHARMACEUTICALS, INC.) 28 August 2014 (28.08.2014) para [0035], [0089]-[0092], [0764]-[0770], [0777]-[0788]	1-6, 8/(1-6), 18-23 --- 7, 8/7, 54-63, 69-79
Y	US 9,040,518 B2 (AQUINO et al.) 26 May 2015 (26.05.2015) col 1, ln 15-20; col 4, ln 25-27; col 57, ln 50-65	7, 8/7, 60, (61-63)/60
Y	DAVIT-SPRAUL et al. 'ATP8B1 and ABCB11 Analysis in 62 Children with Normal Gamma-Glutamyl Transferase Progressive Familial Intrahepatic Cholestasis (PFIC): Phenotypic Differences Between PFIC1 and PFIC2 and Natural History', HEPATOLOGY, 2010, Vol.51, No.5, pp. 1645-1655. abstract; pg 1652, col 2, para 1	54-63, 69-79
A	WO 2017/167935 A1 (GENFIT) 05 October 2017 (05.10.2017) pg 4, ln 1-3; pg 4, ln 18-24; pg 10, ln 25-31; pg 11, ln 16-18	1-8, 18-23, 54-63, 69-79
A	WO 2018/002827 A1 (GLAXOSMITHKLINE INTELLECTUAL PROPERTY (NO.2) LIMITED) 04 January 2018 (04.01.2018) pg 1, ln 20-25; pg 2, ln 6-10; pg 11, ln 1 to pg 12, ln 6	1-8, 18-23, 54-63, 69-79
A	PUBCHEM-CID: 9939892 Create Date: 25 October 2006 (25.10.2006) pages 1-24. pg 2, structure	6, 59

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 May 2020	26 JUN 2020
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Lee Young Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 20/17951

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 9-17, 24-53, 64-68 and 80-112
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.