TREATING LIVER DISORDERS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 62/933,277, filed November 8, 2019, and U.S. Provisional Application No. 63/004,403, filed April 2, 2020, the content of each of which is incorporated herein by reference in its entirety.

FIELD

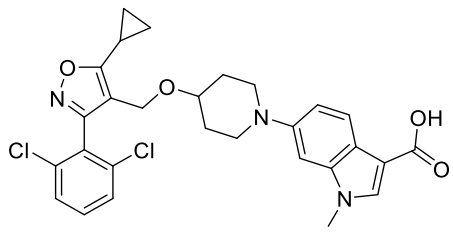
[0002] This invention relates to methods and compositions for treating a liver disorder in a patient.

BACKGROUND

[0003] Fatty liver disease (FLD) encompasses a spectrum of disease states characterized by excessive accumulation of fat in the liver often accompanied with inflammation. FLD can lead to non-alcoholic fatty liver disease (NAFLD), which may be characterized by insulin resistance. If untreated, NAFLD can progress to a persistent inflammatory response or non-alcoholic steatohepatitis (NASH), progressive liver fibrosis, and eventually to cirrhosis. In Europe and the US, NAFLD is the second most common reason for liver transplantation. Accordingly, the need for treatment is urgent, but due to the lack of obvious symptoms to the patient, patients may lack the motivation to maintain treatment regimens, particularly burdensome treatment regimens, such as injected medicines, medications that are administered many times a day, or any that produce dangerous or irritating side effects. There is currently no approved treatment of NASH.

BRIEF SUMMARY

[0003a] In an aspect of the present disclosure, there is provided a use of a compound of Formula (I)

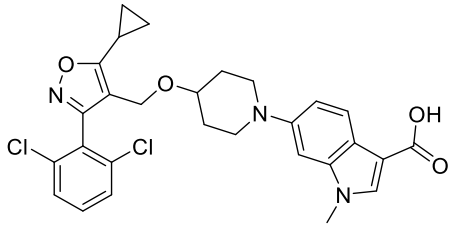


(I)

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a liver disorder in a patient in need thereof, wherein the liver disorder is selected from liver inflammation, liver fibrosis, alcohol induced fibrosis, steatosis, alcoholic steatosis, primary

sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH).

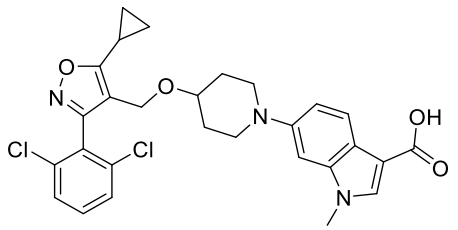
[0003b] In another aspect of the present disclosure, there is provided a use of a Farnesoid X Receptor (FXR) agonist in the manufacture of a medicament for treating a liver disorder in a patient in need thereof, wherein the FXR agonist is a compound of Formula (I)



(I),

or a pharmaceutically acceptable salt thereof, wherein the patient has discontinued one or more prior therapies with another FXR agonist other than a compound of Formula (I) or a pharmaceutically acceptable salt thereof, and wherein the liver disorder is selected from liver inflammation, liver fibrosis, alcohol induced fibrosis, steatosis, alcoholic steatosis, primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH).

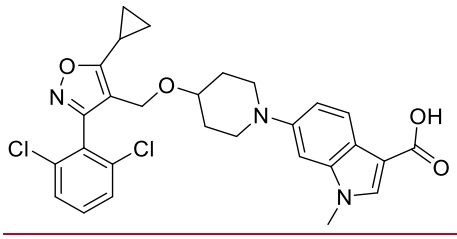
[0003c] In a further aspect of the present disclosure, there is provided a use of a compound of Formula (I)



(I),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for impeding or slowing the progression of non- alcoholic fatty liver disease (NAFLD) to non-alcoholic steatohepatitis (NASH) in a patient in need thereof.

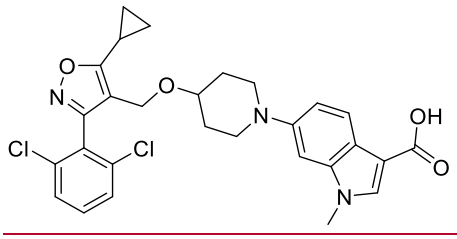
[0003d] In another aspect of the present disclosure, there is provided a use of a compound of Formula (I)



(I),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for impeding or slowing the progression of NASH in a patient in need thereof.

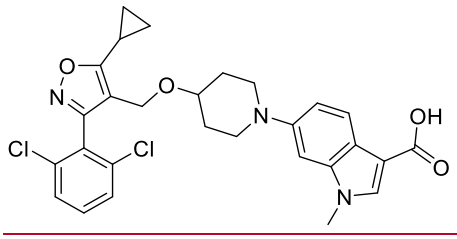
[0003e] In a further aspect of the present disclosure, there is provided a use of a Farnesoid X Receptor (FXR) agonist in the manufacture of a medicament for treating a liver disorder in a patient in need thereof, wherein the FXR agonist is a compound of Formula (I)



(I),

or a pharmaceutically acceptable salt thereof, wherein the FXR agonist preferentially concentrates in liver tissue over one or more of kidney, lung, heart, and skin tissues, and wherein the liver disorder is selected from liver inflammation, liver fibrosis, alcohol induced fibrosis, steatosis, alcoholic steatosis, primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH).

[0003f] In another aspect of the present disclosure, there is provided a use of an FXR agonist in the manufacture of a medicament for treating a liver disorder in a patient in need thereof, wherein the FXR agonist is a compound of Formula (I)

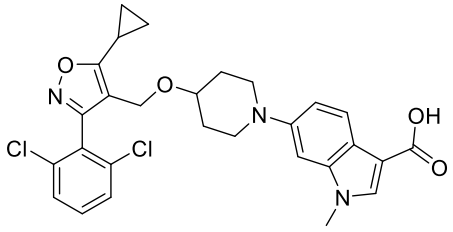


(I),

or a pharmaceutically acceptable salt thereof, wherein the FXR agonist does not result in detectable pruritus in a patient in need thereof, and wherein the liver disorder is selected from

liver inflammation, liver fibrosis, alcohol induced fibrosis, steatosis, alcoholic steatosis, primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH).

[0004] Provided herein are methods of treating a liver disorder in a patient in need thereof comprising administering a therapeutically effective amount of a compound of Formula (I)

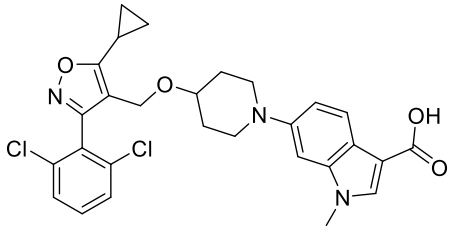


(I)

or a pharmaceutically acceptable salt thereof, wherein the liver disorder is selected from liver inflammation, liver fibrosis, alcohol induced fibrosis, steatosis, alcoholic steatosis, primary

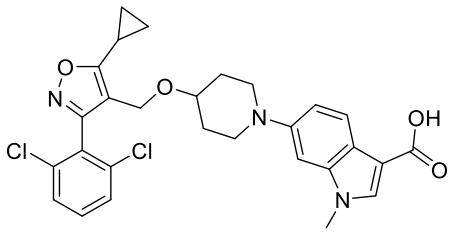
sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH).

[0005] Also provided herein are methods of treating a liver disorder in a patient in need thereof with a Farnesoid X Receptor (FXR) agonist, comprising administering a therapeutically effective amount of the FXR agonist, wherein the FXR agonist is a compound of Formula (I)



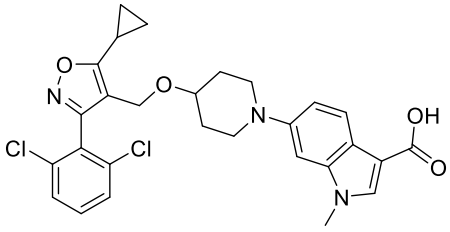
(I), or a pharmaceutically acceptable salt thereof, and wherein the patient has discontinued one or more prior therapies with another FXR agonist other than a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the liver disorder is selected from liver inflammation, liver fibrosis, alcohol induced fibrosis, steatosis, alcoholic steatosis, primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH). In some ~~embodiment~~example<u></u>s, the patient suffered from pruritus during the one or more prior therapies.

[0006] Also provided herein are methods of impeding or slowing the progression of non-alcoholic fatty liver disease (NAFLD) to non-alcoholic steatohepatitis (NASH) in a patient in need thereof comprising administering a therapeutically effective amount of a compound of Formula (I)



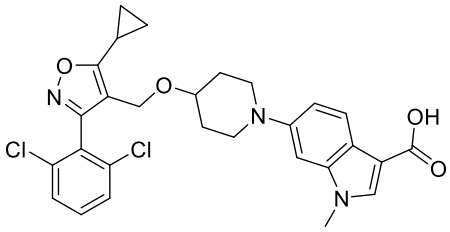
(I), or a pharmaceutically acceptable salt thereof.

[0007] Also provided herein are methods of impeding or slowing the progression of NASH in a patient in need thereof comprising administering a therapeutically effective amount of a compound of Formula (I)



(I), or a pharmaceutically acceptable salt thereof.

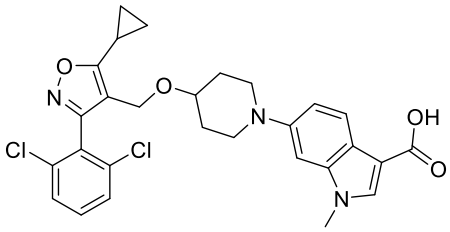
[0008] Also provided herein are methods of treating a liver disorder in a patient in need thereof with a Farnesoid X Receptor (FXR) agonist that preferentially concentrates in liver tissue over one or more of kidney, lung, heart, and skin tissues, the method comprising administering a therapeutically effective amount of the FXR agonist, wherein the FXR agonist is a compound of Formula (I)



(I), or a pharmaceutically acceptable salt thereof, wherein the liver disorder is selected from liver inflammation, liver fibrosis, alcohol induced fibrosis, steatosis, alcoholic steatosis, primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH).

[0009] In some ~~embodiment~~examples, the administration does not result in pruritus in the patient greater than Grade 2 in severity. In some ~~embodiment~~examples, the administration does not result in pruritus in the patient greater than Grade 1 in severity. In some ~~embodiment~~examples, the administration does not result in pruritus in the patient.

[0010] Also provided herein are methods of treating a liver disorder with an FXR agonist that does not result in detectable pruritus in a patient in need thereof, the method comprising administering a therapeutically effective amount of the FXR agonist, wherein the FXR agonist is a compound of Formula (I)



(I), or a pharmaceutically acceptable salt thereof, wherein the liver disorder is selected from liver inflammation, liver fibrosis, alcohol induced fibrosis,

steatosis, alcoholic steatosis, primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH).

[0011] In some ~~embodiment~~examples, the liver disorder is NAFLD. In some ~~embodiment~~examples, the liver disorder is NASH. In some ~~embodiment~~examples, the liver disorder is PSC. In some ~~embodiment~~examples, the liver disorder is PBC.

[0012] In some ~~embodiment~~examples, the administration results in a liver concentration to plasma concentration ratio of the compound of Formula (I) of 10 or greater.

[0013] In some ~~embodiment~~examples, the therapeutically effective amount is 0.5 μg/day – 600 mg/day. In some ~~embodiment~~examples, the therapeutically effective amount is 0.5 μg/day – 20 mg/day. In some ~~embodiment~~examples, the therapeutically effective amount is 0.5 μg/day – 4 mg/day.

[0014] In some ~~embodiment~~examples, the administration comprises administering the compound of Formula (I), or a pharmaceutically acceptable salt thereof, daily for a treatment period of one or more weeks. In some ~~embodiment~~examples, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered once daily or twice daily. In some ~~embodiment~~examples, the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, administered on day 1 of the treatment period is greater than or equal to the amount administered on all subsequent days of the treatment period. In some ~~embodiment~~examples, the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, administered on day 1 of the treatment period is equal to the amount administered on all subsequent days of the treatment period. In some ~~embodiment~~examples, the treatment period is one or more months. In some ~~embodiment~~examples, the treatment period is the remaining lifespan of the patient.

[0015] In some ~~embodiment~~examples, the patient is obese. In some ~~embodiment~~examples, the patient is not obese. In some ~~embodiment~~examples, the patient also has diabetes mellitus and/or a cardiovascular disorder. In some ~~embodiment~~examples, the patient is at risk for developing an adverse effect affecting one or more of the kidneys, lung, heart, and skin. In some ~~embodiment~~examples, the patient is 2-17 years old. In some ~~embodiment~~examples, the patient is 18-54 years old. In some ~~embodiment~~examples, the patient is 65 or more years old. In some ~~embodiment~~examples, the patient has had a liver transplant. In some ~~embodiment~~examples, the patient's alkaline phosphatase, gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels are elevated.

[0016] In some ~~embodiment~~examples, the method does not comprise administering an antihistamine, an immunosuppressant, a steroid, rifampicin, an opioid antagonist, or a selective serotonin reuptake inhibitor (SSRI).

[0017] In some ~~embodiment~~examples, NAS score of the patent is decreased upon administration. In some ~~embodiment~~examples, TGR5 signaling is not activated upon administration.

[0018] In some ~~embodiment~~examples, the administration results in decreased level of expression of a marker of fibrosis. In some ~~embodiment~~examples, the expression level of Ccr2, Col1a1, Col1a2, Col1a3, Cxcr3, Dcn, Hgf, Il1a, Inhbe, Lox, Loxl1, Loxl2, Loxl3, Mmp2, Pdgfb, Plau, Serpine1, Perpinh1, Snai, Tgfb1, Tgfb3, Thbs1, Thbs2, Timp2, and/or Timp3 is reduced.

[0019] In some ~~embodiment~~examples, the administration results in decreased level of expression of a marker of liver inflammation. In some ~~embodiment~~examples, the level of Adgre1, Ccr2, Ccr5, Il1A, and/or Tlr4 is reduced.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] FIG. 1A shows plasma concentrations of Compound I at various time points after intravenous (IV) administration to rats (1 mg/kg), dogs (1 mg/kg) and monkeys (0.3 mg/kg).

[0021] FIG. 1B shows plasma concentrations of Compound I at various time points after oral administration to mice (10 mg/kg), rats (10 mg/kg), dogs (3 mg/kg) and monkeys (5 mg/kg).

[0022] FIG. 2A shows the liver to plasma ratio of the concentration of Compound I, obeticholic acid (OCA), cilofexor, or tropifexor after 2 mg/kg IV administration to Sprague-Dawley (SD) rats.

[0023] FIG. 2B shows the tissue to plasma ratio of the concentration of Compound I for kidney, lung, and liver after 2 mg/kg IV administration of Compound I to SD rats with or without co-administration of rifampicin.

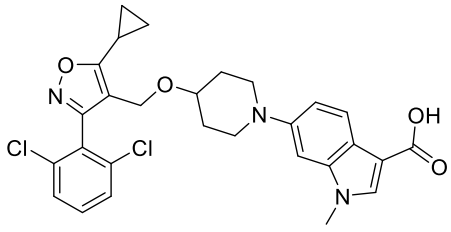
[0024] FIG. 3 shows the tissue distribution of radiolabeled Compound I in plasma, liver, small intestine, cecum, kidney, lungs, heart, and skin after 5 mg/kg oral administration of Compound I to Long-Evans rats.

[0025] FIG. 4 shows the pharmacodynamics of Compound I administration, as measured by 7-alpha-hydroxy-4-cholesten-3-one (7α-C4), after administration of 0.3 mg/kg, 1 mg/kg or 5 mg/kg oral dose to cynomolgus monkeys.

CLAIMS

What is claimed is:

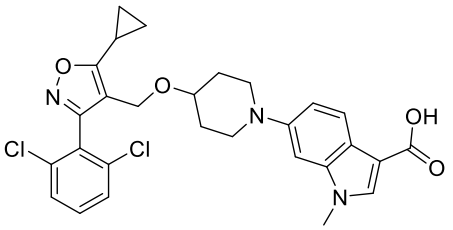
1. Use ~~A method of treating a liver disorder in a patient in need thereof comprising administering a therapeutically effective amount~~ of a compound of Formula (I)



(I)

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a liver disorder in a patient in need thereof, wherein the liver disorder is selected from liver inflammation, liver fibrosis, alcohol induced fibrosis, steatosis, alcoholic steatosis, primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH).

2. Use of ~~A method of treating a liver disorder in a patient in need thereof with~~ a Farnesoid X Receptor (FXR) agonist in the manufacture of a medicament for treating a liver disorder in a patient in need thereof, ~~comprising administering a therapeutically effective amount of the FXR agonist,~~ wherein the FXR agonist is a compound of Formula (I)

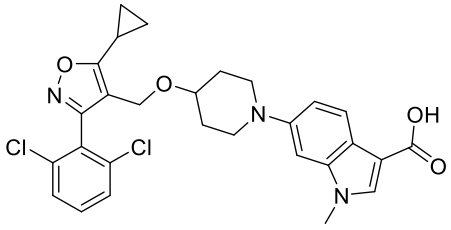


(I),

or a pharmaceutically acceptable salt thereof, ~~and~~ wherein the patient has discontinued one or more prior therapies with another FXR agonist other than a compound of Formula (I) or a pharmaceutically acceptable salt thereof, and wherein the liver disorder is selected from liver inflammation, liver fibrosis, alcohol induced fibrosis, steatosis, alcoholic steatosis, primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH).

3. The ~~method~~use of claim~~s~~ 2, wherein the patient suffered from pruritus during the one or more prior therapies.

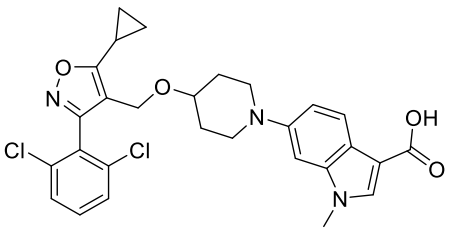
4. Use of ~~A method of impeding or slowing the progression of non- alcoholic fatty liver disease (NAFLD) to non-alcoholic steatohepatitis (NASH) in a patient in need thereof comprising administering a therapeutically effective amount of~~ a compound of Formula (I)



(I),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for impeding or slowing the progression of non- alcoholic fatty liver disease (NAFLD) to non-alcoholic steatohepatitis (NASH) in a patient in need thereof.

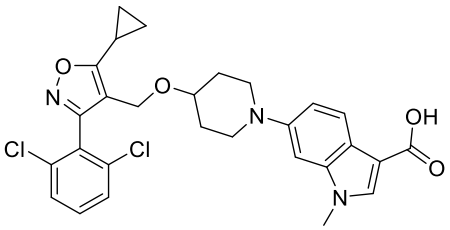
5. Use ~~A method of impeding or slowing the progression of NASH in a patient in need thereof comprising administering a therapeutically effective amount~~ of a compound of Formula (I)



(I),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for impeding or slowing the progression of NASH in a patient in need thereof.

6. Use of ~~A method of treating a liver disorder in a patient in need thereof with~~ a Farnesoid X Receptor (FXR) agonist in the manufacture of a medicament for treating a liver disorder in a patient in need thereof, ~~that preferentially concentrates in liver tissue over one or more of kidney, lung, heart, and skin tissues, the method comprising administering a therapeutically effective amount of the FXR agonist,~~ wherein the FXR agonist is a compound of Formula (I)



(I),

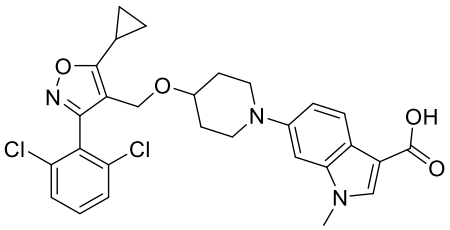
or a pharmaceutically acceptable salt thereof, wherein the FXR agonist preferentially concentrates in liver tissue over one or more of kidney, lung, heart, and skin tissues, and wherein the liver disorder is selected from liver inflammation, liver fibrosis, alcohol induced fibrosis, steatosis, alcoholic steatosis, primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH).

7. The ~~method~~use of any one of claims 1-6, wherein the compound, or a pharmaceutically acceptable salt thereof, is to be administered to the patient, and wherein the administration does not result in pruritus in the patient greater than Grade 2 in severity.

8. The ~~method~~use of any one of claims 1-7, wherein the compound, or a pharmaceutically acceptable salt thereof, is to be administered to the patient, and wherein the administration does not result in pruritus in the patient greater than Grade 1 in severity.

9. The ~~method~~use of any one of claims 1-8, wherein the compound, or a pharmaceutically acceptable salt thereof, is to be administered to the patient, and wherein the administration does not result in pruritus in the patient.

10. Use of ~~A method of treating a liver disorder with~~ an FXR agonist in the manufacture of a medicament for treating a liver disorder ~~that does not result in detectable pruritus~~ in a patient in need thereof, ~~the method comprising administering a therapeutically effective amount of the FXR agonist,~~ wherein the FXR agonist is a compound of Formula (I)



(I),

or a pharmaceutically acceptable salt thereof, wherein the FXR agonist does not result in detectable pruritus in a patient in need thereof, and wherein the liver disorder is selected from liver inflammation, liver fibrosis, alcohol induced fibrosis, steatosis, alcoholic steatosis, primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH).

11. The ~~method~~use of any one of claims 1-3, or 6-10, wherein the liver disorder is NAFLD.

12. The ~~method~~use of any one of claims 1-3, or 6-10, wherein the liver disorder is NASH.

13. The ~~method~~use of any one of claims 1-3, or 6-10, wherein the liver disorder is PSC.

14. The ~~method~~use of any one of claims 1-3, or 6-10, wherein the liver disorder is PBC.

15. The ~~method~~use of any one of claims 1-14, wherein the compound, or a pharmaceutically acceptable salt thereof, is to be administered to the patient, and wherein the administration results in a liver concentration to plasma concentration ratio of the compound of Formula (I) of 10 or greater.

16. The ~~method~~use of any one of claims 1-15, wherein a therapeutically effective amount of the compound, or a pharmaceutically acceptable salt thereof, is to be administered to the patient, and wherein the therapeutically effective amount is 0.5 µg/day – 600 mg/day.

17. The ~~method~~use of any one of claims 1-16, wherein a therapeutically effective amount of the compound, or a pharmaceutically acceptable salt thereof, is to be administered to the patient, and wherein the therapeutically effective amount is 0.5 µg/day – 20 mg/day.

18. The ~~method~~use of any one of claims 1-17, wherein a therapeutically effective amount of the compound, or a pharmaceutically acceptable salt thereof, is to be administered to the patient, and wherein the therapeutically effective amount is 0.5 µg/day – 4 mg/day.

19. The ~~method~~use of any one of claims 1-18, wherein ~~the administration comprises administering~~ the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is to be administered to the patient daily for a treatment period of one or more weeks.

20. The ~~method~~use of claim 19, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is to be administered once daily or twice daily.

21. The ~~method~~use of claim 19 or 20, wherein the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is to be administered on day 1 of the treatment period is greater than or equal to the amount is to be administered on all subsequent days of the treatment period.

22. The ~~method~~use of any one of claims 19-21, wherein the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is to be administered on day 1 of the treatment period is equal to the amount is to be administered on all subsequent days of the treatment period.

23. The ~~method~~use of any one of claims 1-22, wherein the treatment period is one or more months.

24. The ~~method~~use of any one of claims 1-23, wherein the treatment period is the remaining lifespan of the patient.

25. The ~~method~~use of any one of claims 1-24, wherein the patient is obese.

26. The ~~method~~use of any one of claims 1-24, wherein the patient is not obese.

27. The ~~method~~use of any one of claims 1-26, wherein the patient also has diabetes mellitus and/or a cardiovascular disorder.

28. The ~~method~~use of any one of claims 1-27, wherein the patient is at risk for developing an adverse effect affecting one or more of the kidney, lung, heart, and skin.

29. The ~~method~~use of any one of claims 1-28, wherein the patient is 2-17 years old.

30. The ~~method~~use of any one of claims 1-28, wherein the patient is 18-54 years old.

31. The ~~method~~use of any one of claims 1-28, wherein the patient is 65 or more years old.

32. The ~~method~~use of any one of claims 1-31, wherein the patient has had a liver transplant.

33. The ~~method~~use of any one of claims 1-32, wherein the patient's alkaline phosphatase, gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels are elevated.

34. The ~~method~~use of any one of claims 1-33, wherein ~~the method does not comprise administering~~ an antihistamine, an immunosuppressant, a steroid, rifampicin, an opioid antagonists, or a selective serotonin reuptake inhibitor (SSRI) is not to be administered.

35. The ~~method~~use of any one of claims 1-34, wherein the NAS score of the patient is decreased.

36. The ~~method~~use of any one of claims 1-35, wherein TGR5 signaling is not activated.

37. The ~~method~~use of any one of claims 1-36, wherein the expression level of a marker of fibrosis is decreased.

38. The ~~method~~use of any one of claims 1-37, wherein the expression level of Ccr2, Col1a1, Col1a2, Col1a3, Cxcr3, Dcn, Hgf, Il1a, Inhbe, Lox, Loxl1, Loxl2, Loxl3, Mmp2, Pdgfb, Plau, Serpine1, Perpinh1, Snai, Tgfb1, Tgfb3, Thbs1, Thbs2, Timp2, and/or Timp3 is reduced.

39. The ~~method~~use of any one of claims 1-38, wherein the expression level of a marker of liver inflammation is decreased.

40. The ~~method~~use of any one of claims 1-39, wherein the level of Adgre1, Ccr2, Ccr5, Il1A, and/or Tlr4 is reduced.