

Combination therapy for the prevention and/or the treatment of a liver disease**Field of the invention**

The present disclosure provides a drug combination and a method for the prevention and/or
5 the treatment of a liver disease, in particular for the prevention and/or the treatment of non-alcoholic fatty liver disease.

Background of the invention

Non-alcoholic fatty liver disease (NAFLD), which has also recently been referred to as
metabolic-associated fatty liver disease (MAFLD), is excessive fat build-up in the liver without
10 another clear cause such as alcohol use. There are two types: non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH) / metabolic-associated steatohepatitis (MASH), with the latter also including liver inflammation. NAFLD is the most common liver disorder worldwide and is present in approximately 25% of the world's population (Nutr Clin Pract 2020; Vol.35, n°1, pages 72-84). NAFLD usually does not progress to NASH. However,
15 when NAFLD does progress to NASH, it may eventually lead to complications such as fibrosis, cirrhosis, liver cancer, liver failure, or cardiovascular disease. Because of the devastating complications and comorbidities, NAFLD is a very costly disease for the healthcare system, with estimated annual direct medical costs exceeding \$100 billion in the United States alone. Yet, as of today, there is no approved treatment for NAFLD or NASH.
20 Lanifibranor (CAS n° 927961-18-0) is a pan-PPAR agonist which is currently in clinical development for the treatment of patients with non-alcoholic steatohepatitis (NASH). It is described in example 117 of WO 2007/026097 where it is obtained as a pale-yellow powder having a melting point of 74-80°C.

In recent years, combining GLP-1 and GIP receptor modulators has received much attention
25 with the purpose of achieving substantial body weight reduction while maintaining optimal glucose control. GLP-1 (glucagon-like peptide-1), produced and secreted by intestinal L-cells in response to nutrients, improves glucose homeostasis, while simultaneously lowering body weight by reducing energy intake. Several long-acting GLP-1 receptor agonists have been clinically approved for the treatment of type 2 diabetes and recently also for the treatment of
30 obesity (Saxenda® and Wegovy®). Glucose-dependent insulintropic polypeptide (more commonly known earlier as gastric inhibitory polypeptide or gastric inhibitory peptide), abbreviated as GIP, is an inhibiting hormone of the secretin family of hormones. While it is a weak inhibitor of gastric acid secretion, its main role, being an incretin, is to stimulate insulin secretion. GIP, along with GLP-1), belongs to a class of molecules referred to as incretins,
35 which stimulate insulin release on oral food intake.

It has now been found that the combined administration of lanifibranor and a GLP-1/GIP dual receptor agonist is useful for preventing and/or treating a liver disease.

Summary of the invention

5 In one aspect, the present disclosure provides a product comprising (i) lanifibranor or a deuterated form thereof and (ii) a GLP-1/GIP dual receptor agonist.

In another aspect, the present disclosure provides a combination of (i) lanifibranor or a deuterated form thereof and (ii) a GLP-1/GIP dual receptor agonist for use in the prevention and/or the treatment of a liver disease.

10 In yet another aspect, the present disclosure provides a method of treating a liver disease, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, applicable to all aspects of the present disclosure, the GLP-1/GIP dual receptor agonist is selected from tirzepatide, VK2735, MAR709 and CT-388.

15 In some embodiments, applicable to all aspects of the present disclosure, the liver disease is selected from cirrhosis, liver fibrosis, liver steatosis, fatty liver disease, acute decompensation, acute decompensation of cirrhosis, acute-on-chronic liver failure (ACLF), acute liver failure (ALF), decompensated cirrhosis, compensated cirrhosis, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), metabolic-associated fatty liver disease (MAFLD), metabolic-associated steatohepatitis (MASH), non-cirrhotic non-alcoholic fatty liver disease, non-cirrhotic non-alcoholic steatohepatitis, non-cirrhotic metabolic-associated fatty liver disease, non-cirrhotic metabolic-associated steatohepatitis, autoimmune cholangitis, primary biliary cholangitis, primary sclerosing cholangitis, autoimmune cholangiopathy, hepatocarcinoma, liver cirrhosis and a combination of these diseases. In
20
25 some embodiments, applicable to all aspects of the disclosure, the liver disease can be associated with diabetes, and in particular with type 2 diabetes.

In some embodiments, applicable to all aspects of the present disclosure, lanifibranor or a deuterated form thereof and the GLP-1/GIP dual receptor agonist are intended to be administered simultaneously, sequentially or over a period of time.

Description of the figures

Figure 1 shows hepatic fatty acids levels in animals fed with a HFCC/CDX diet and treated with lanifibranor alone, with tirzepatide alone, and with a combination of lanifibranor and tirzepatide.

- 5 Figure 2 shows hepatic triglyceride levels in animals fed with a HFCC/CDX diet and treated with lanifibranor alone, with tirzepatide alone, and with a combination of lanifibranor and tirzepatide.

- Figure 3 shows the steatosis score in animals fed with a HFCC/CDX diet and treated with lanifibranor alone, with tirzepatide alone, and with a combination of lanifibranor and
10 tirzepatide.

Figure 4 shows the inflammation score in animals fed with a HFCC/CDX diet and treated with lanifibranor alone, with tirzepatide alone, and with a combination of lanifibranor and tirzepatide.

- Figure 5 shows the fibrosis score in animals fed with a HFCC/CDX diet and treated with
15 lanifibranor alone, with tirzepatide alone, and with a combination of lanifibranor and tirzepatide.

Figure 6 shows the total score (steatosis + inflammation + fibrosis) in animals fed with a HFCC/CDX diet and treated with lanifibranor alone, with tirzepatide alone, and with a combination of lanifibranor and tirzepatide.

- 20 Figure 7 shows the % of liver fibrosis over the total liver area, as evaluated by picosirius red staining, in animals fed with a HFCC/CDX diet and treated with lanifibranor alone, with tirzepatide alone, and with a combination of lanifibranor and tirzepatide.

Detailed description of the invention

- As used herein, the articles including "a" and "an", are understood to mean one or more of
25 what is claimed or described.

As used herein the expression "about xx" includes the value "xx".

As used herein, the expression "from xx to yy" includes the end points xx and yy of the range.

- As used herein, the term "prevention" or "prophylaxis" or "preventative treatment" or
30 "prophylactic treatment" comprises a treatment leading to the prevention of a disease as well as a treatment reducing and/or delaying the incidence of a disease or the risk of it occurring.

- As used herein, the term "treatment" or "treating" refers to any process, action, application, therapy, or the like, wherein the patient is under aid, in particular, medical, or veterinarian
35 aid with the object of improving the patient's condition, in particular leading to a cure or a

treatment which alleviates, improves and/or eliminates, reduces and/or stabilizes the symptoms of a disease or the suffering that it causes, either directly or indirectly.

As used herein, "patient" or "subject" refers to a human individual or an animal different from a human. The patient is for example a human or an animal liable to have a liver disease or suffering from such a disease. The patient is advantageously a human being. The patient

5 may be a child (human patient 18 years old or less) or an adult (human patient more than 18 years old). In another embodiment, the subject is a non-human animal including, but are not limited to dog, cat, guinea pig, rabbit, rat, mouse, horse, cattle, bear, cow, ape, monkey, orangutan, and chimpanzee, and so on. In the context of the present disclosure the terms

10 "patient" and "subject" are used interchangeably.

As used herein, the term "acute decompensation" refers to an abrupt deterioration of liver function in patients with advanced chronic liver diseases, compensated cirrhosis or stable decompensated cirrhosis requiring immediate hospitalization. At hospital admission, patients with acute decompensation have multiple symptoms including, severe ascites, hepatic

15 encephalopathy, variceal bleeding associated or not with sepsis and/or impaired renal function and/or coagulopathy and/or impaired cardiovascular function and/or impaired respiratory function. Acute decompensation is a life-threatening condition with an overall mortality rate of 11% at 28-Days. In one embodiment, "acute decompensation" refers to acute decompensation of cirrhosis.

20 As used herein, "deuterated form of lanifibranor" refers to a compound having the structure of lanifibranor in which one or more hydrogen atoms is/are replaced by a deuterium atom. In particular, "deuterated form of lanifibranor" refers to a compound having the structure of lanifibranor in which at least one hydrogen atom is replaced by a deuterium atom. As used herein, the expressions "deuterated form of lanifibranor" and "deuterated derivative of

25 lanifibranor" can be used interchangeably.

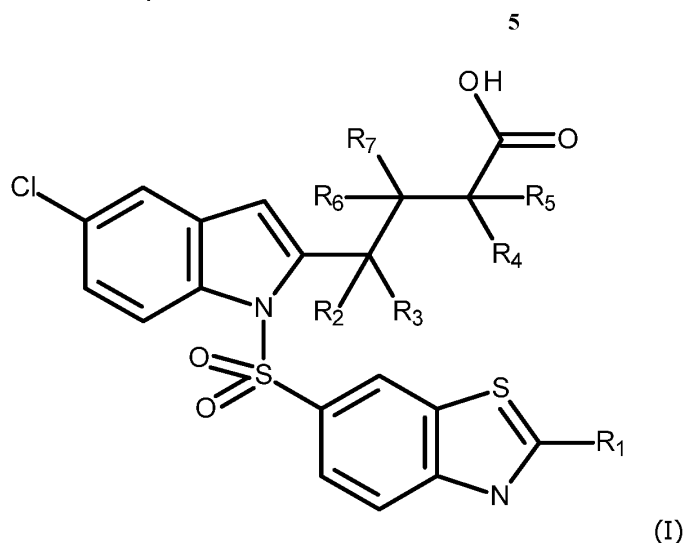
In the context of the present disclosure, the various embodiments described herein can be combined.

In one aspect, the present disclosure provides a product comprising (i) lanifibranor or a deuterated form thereof, and (ii) a GLP-1/GIP dual receptor agonist.

30 Lanifibranor (CAS n° 927961-18-0), also called IVA337 is a pan-PPAR agonist. In some embodiments, lanifibranor is in crystalline form. Examples of crystalline form of lanifibranor have been described in WO2023/194339, in WO2023/016319, in WO2022/122014, in WO2022/261410 or in WO2022/258060, all incorporated herein by reference.

In some embodiments, a deuterated form of lanifibranor/deuterated derivative of lanifibranor

35 is a compound of formula (I):



- wherein at least one of the groups R_1 to R_7 is a deuterium (D) atom and the other groups R_1 to R_7 are hydrogen (H) atoms, as described in WO2020/021215. In some aspects, at least group R_1 is D. In some aspects at least one of the groups R_2 to R_7 is D, notably at least one of the groups R_2 and R_3 and/or at least one of the groups R_4 and R_5 and/or at least one of the groups R_6 and R_7 is D. In a preferred aspect each of R_2 , R_3 , R_4 , R_5 , R_6 and R_7 is D. Preferred compounds of formula (I) include 4-(1-(2-deuterio-1,3-benzothiazol-6-yl)sulfonyl)-5-chloro-1H-indol-2-yl)butanoic acid and 4-[1-(1,3-benzothiazol-6-ylsulfonyl)-5-chloro-indol-2-yl]-2,2,3,3,4,4-hexadeuteriobutanoic acid.
- In some embodiments, lanifibranor or a deuterated form thereof is in the form of one of its pharmaceutically acceptable salts or solvates. The term "solvate" is used herein to describe a molecular complex comprising lanifibranor or a deuterated form thereof and one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term "hydrate" is employed when said solvent is water. Pharmaceutically acceptable salts of lanifibranor or a deuterated form thereof include base addition salts thereof. Base addition salts may be prepared from inorganic and organic bases. Examples of inorganic bases include sodium hydroxide, potassium hydroxide, magnesium hydroxide and calcium hydroxide. Examples of organic bases include amines, amino alcohols, basic amino acids such as lysine or arginine, and quaternary ammonium compounds such as betaine or choline.
- In some embodiments, the GLP-1/GIP dual receptor agonist is selected from tirzepatide, VK2735, MAR709 and CT-388, preferably the GLP-1/GIP dual receptor agonist is tirzepatide. In some embodiments, the liver disease is selected from cirrhosis, liver fibrosis, liver steatosis, fatty liver disease, acute decompensation, acute decompensation of cirrhosis, acute-on-chronic liver failure (ACLF), acute liver failure (ALF), decompensated cirrhosis, compensated cirrhosis, non-alcoholic fatty liver disease (NAFLD), non-alcoholic

steatohepatitis (NASH), metabolic-associated fatty liver disease (MAFLD), metabolic-associated steatohepatitis (MASH), non-cirrhotic non-alcoholic fatty liver disease, non-cirrhotic non-alcoholic steatohepatitis, non-cirrhotic metabolic-associated fatty liver disease, non-cirrhotic metabolic-associated steatohepatitis, autoimmune cholangitis, primary biliary
5 cholangitis, primary sclerosing cholangitis, autoimmune cholangiopathy, hepatocarcinoma, liver cirrhosis and a combination of these diseases.. The liver disease is advantageously selected from NAFLD, NASH, MAFLD and MASH.

In some embodiments, the liver disease can be selected from non-alcoholic fatty liver disease (NAFLD) with liver fibrosis, non-alcoholic steatohepatitis (NASH) with liver fibrosis,
10 metabolic-associated fatty liver disease (MAFLD) with liver fibrosis, metabolic-associated steatohepatitis (MASH) with liver fibrosis, non-alcoholic steatohepatitis with liver fibrosis, metabolic-associated steatohepatitis with liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with liver fibrosis. In particular, liver fibrosis can be determined using fibrosis score.

15 Fibrosis score comprises five different stages of liver fibrosis:

- F0 corresponding to absence of liver scarring (also called F0 stage of liver fibrosis),
- F1 corresponding to mild liver scarring (also called "mild liver fibrosis" or F1 stage of liver fibrosis),
- F2 corresponding to moderate liver scarring (also called "moderate liver fibrosis" or
20 F2 stage of liver fibrosis),
- F3 corresponding to advanced liver scarring (also called "advanced liver fibrosis" or F3 stage of liver fibrosis),
- F4 corresponding to severe liver scarring (also called "severe liver fibrosis" F4 stage of liver fibrosis or cirrhosis).

25 As used herein, absence of liver fibrosis is stage F0 fibrosis. As used herein, mild liver fibrosis is F1 stage of liver fibrosis. As used herein, moderate liver fibrosis is F2 stage of liver fibrosis. As used herein, advanced liver fibrosis is F3 stage of liver fibrosis. As used herein, severe liver fibrosis is F4 stage of liver fibrosis.

As used herein, absence to mild liver fibrosis is from F0 to F1 stage of liver fibrosis. As used
30 herein, mild to moderate liver fibrosis is from F1 to F2 stage of liver fibrosis. As used herein, moderate to advanced liver fibrosis is from F2 to F3 stage of liver fibrosis. As used herein, advanced to severe liver fibrosis is from F3 to F4 stage of liver fibrosis.

In some embodiments, the liver disease can be selected from non-alcoholic fatty liver disease (NAFLD) with F0 stage of liver fibrosis, non-alcoholic steatohepatitis (NASH) with F0
35 stage of liver fibrosis, metabolic-associated fatty liver disease (MAFLD) with F0 stage of liver

fibrosis, metabolic-associated steatohepatitis (MASH) with F0 stage of liver fibrosis, non-alcoholic steatohepatitis with F0 stage of liver fibrosis, metabolic-associated steatohepatitis with F0 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F0 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F0 stage of liver fibrosis.

- 5 In some embodiments, the liver disease is non-cirrhotic non-alcoholic steatohepatitis (NASH) and fibrosis 0 (F0) stage of liver fibrosis. In some embodiments, the liver disease is non-cirrhotic metabolic-associated steatohepatitis (MASH) and fibrosis 0 (F0) stage of liver fibrosis. In some embodiments, the liver disease is non-cirrhotic non-alcoholic steatohepatitis (NASH) with F0 stage of liver fibrosis. In some embodiments, the liver disease is non-cirrhotic metabolic-associated steatohepatitis (MASH) with F0 stage of liver fibrosis. In some
- 10 embodiments, the liver disease can be selected from non-alcoholic fatty liver disease (NAFLD) with absence of liver fibrosis, non-alcoholic steatohepatitis (NASH) with absence of liver fibrosis, metabolic-associated fatty liver disease (MAFLD) with absence of liver fibrosis, metabolic-associated steatohepatitis (MASH) with absence of liver fibrosis, non-alcoholic steatohepatitis with absence of liver fibrosis, metabolic-associated steatohepatitis with absence of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis absence of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with absence of liver fibrosis.

- In some embodiments, the liver disease can be selected from non-alcoholic fatty liver disease (NAFLD) with F0/F1 stage of liver fibrosis, non-alcoholic steatohepatitis (NASH) with
- 20 F0/F1 stage of liver fibrosis, metabolic-associated fatty liver disease (MAFLD) with F0/F1 stage of liver fibrosis, metabolic-associated steatohepatitis (MASH) with F0/F1 stage of liver fibrosis, non-alcoholic steatohepatitis with F0/F1 stage of liver fibrosis, metabolic-associated steatohepatitis with F0/F1 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F0/F1 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with
- 25 F0/F1 stage of liver fibrosis. In some embodiments, the liver disease is non-cirrhotic non-alcoholic steatohepatitis (NASH) with F0/F1 stage of liver fibrosis. In some embodiments, the liver disease is non-cirrhotic metabolic-associated steatohepatitis (MASH) with F0/F1 stage of liver fibrosis.

- In some embodiments, the liver disease can be selected from non-alcoholic fatty liver disease (NAFLD) with F1 stage of liver fibrosis, non-alcoholic steatohepatitis (NASH) with F1
- 30 stage of liver fibrosis, metabolic-associated fatty liver disease (MAFLD) with F1 stage of liver fibrosis, metabolic-associated steatohepatitis (MASH) with F1 stage of liver fibrosis, non-alcoholic steatohepatitis with F1 stage of liver fibrosis, metabolic-associated steatohepatitis with F1 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F1 stage of
- 35 liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F1 stage of liver fibrosis.

In some embodiments, the liver disease is non-cirrhotic non-alcoholic steatohepatitis (NASH) and fibrosis 1 (F1) stage of liver fibrosis. In some embodiments, the liver disease is non-cirrhotic metabolic-associated steatohepatitis (MASH) and fibrosis 1 (F1) stage of liver fibrosis. In some embodiments, the liver disease is non-cirrhotic non-alcoholic steatohepatitis (NASH) with F1 stage of liver fibrosis. In some embodiments, the liver disease is non-cirrhotic metabolic-associated steatohepatitis (MASH) with F1 stage of liver fibrosis. In some embodiments, the liver disease can be selected from non-alcoholic fatty liver disease (NAFLD) with mild liver fibrosis, non-alcoholic steatohepatitis (NASH) with mild liver fibrosis, metabolic-associated fatty liver disease (MAFLD) with mild liver fibrosis, metabolic-associated steatohepatitis (MASH) with mild liver fibrosis, non-alcoholic steatohepatitis with mild liver fibrosis, metabolic-associated steatohepatitis with mild liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis mild liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with mild liver fibrosis.

In some embodiments, the liver disease can be selected from non-alcoholic fatty liver disease (NAFLD) with F1/F2 stage of liver fibrosis, non-alcoholic steatohepatitis (NASH) with F1/F2 stage of liver fibrosis, metabolic-associated fatty liver disease (MAFLD) with F1/F2 stage of liver fibrosis, metabolic-associated steatohepatitis (MASH) with F1/F2 stage of liver fibrosis, non-alcoholic steatohepatitis with F1/F2 stage of liver fibrosis, metabolic-associated steatohepatitis with F1/F2 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F1/F2 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F1/F2 stage of liver fibrosis. In some embodiments, the liver disease is non-cirrhotic non-alcoholic steatohepatitis (NASH) and fibrosis 1/2 (F1/F2) stage of liver fibrosis. In some embodiments, the liver disease is non-cirrhotic metabolic-associated steatohepatitis (MASH) and fibrosis 1/2 (F1/F2) stage of liver fibrosis. In some embodiments, the liver disease is non-cirrhotic non-alcoholic steatohepatitis (NASH) with F1/F2 stage of liver fibrosis. In some embodiments, the liver disease is non-cirrhotic metabolic-associated steatohepatitis (MASH) with F1/F2 stage of liver fibrosis. In some embodiments, the liver disease can be selected from non-alcoholic fatty liver disease (NAFLD) with mild to moderate liver fibrosis, non-alcoholic steatohepatitis (NASH) with mild to moderate liver fibrosis, metabolic-associated fatty liver disease (MAFLD) with mild to moderate liver fibrosis, metabolic-associated steatohepatitis (MASH) with mild to moderate liver fibrosis, non-alcoholic steatohepatitis with mild to moderate liver fibrosis, metabolic-associated steatohepatitis with mild to moderate liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis mild to moderate liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with mild to moderate liver fibrosis.

In some embodiments, the liver disease can be selected from non-alcoholic fatty liver disease (NAFLD) with F2 stage of liver fibrosis, non-alcoholic steatohepatitis (NASH) with F2 stage of liver fibrosis, metabolic-associated fatty liver disease (MAFLD) with F2 stage of liver fibrosis, metabolic-associated steatohepatitis (MASH) with F2 stage of liver fibrosis, non-
5 alcoholic steatohepatitis with F2 stage of liver fibrosis, metabolic-associated steatohepatitis with F2 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F2 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F2 stage of liver fibrosis. In some embodiments, the liver disease is non-cirrhotic non-alcoholic steatohepatitis (NASH) and fibrosis 2 (F2) stage of liver fibrosis. In some embodiments, the liver disease is non-
10 cirrhotic metabolic-associated steatohepatitis (MASH) and fibrosis 2 (F2) stage of liver fibrosis. In some embodiments, the liver disease is non-cirrhotic non-alcoholic steatohepatitis (NASH) with F2 stage of liver fibrosis. In some embodiments, the liver disease is non-cirrhotic metabolic-associated steatohepatitis (MASH) with F2 stage of liver fibrosis. In some embodiments, the liver disease can be selected from non-alcoholic fatty liver disease
15 (NAFLD) with moderate liver fibrosis, non-alcoholic steatohepatitis (NASH) with moderate liver fibrosis, metabolic-associated fatty liver disease (MAFLD) with moderate liver fibrosis, metabolic-associated steatohepatitis (MASH) with moderate liver fibrosis, non-alcoholic steatohepatitis with moderate liver fibrosis, metabolic-associated steatohepatitis with moderate liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis moderate liver fibrosis,
20 non-cirrhotic metabolic-associated steatohepatitis with moderate liver fibrosis. In some embodiments, the liver disease can be selected from non-alcoholic fatty liver disease (NAFLD) with F2/F3 stage of liver fibrosis, non-alcoholic steatohepatitis (NASH) with F2/F3 stage of liver fibrosis, metabolic-associated fatty liver disease (MAFLD) with F2/F3 stage of liver fibrosis, metabolic-associated steatohepatitis (MASH) with F2/F3 stage of liver
25 fibrosis, non-alcoholic steatohepatitis with F2/F3 stage of liver fibrosis, metabolic-associated steatohepatitis with F2/F3 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F2/F3 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F2/F3 stage of liver fibrosis. In some embodiments, the liver disease is non-cirrhotic non-alcoholic steatohepatitis (NASH) and fibrosis 2/3 (F2/F3) stage of liver fibrosis. In some
30 embodiments, the liver disease is non-cirrhotic metabolic-associated steatohepatitis (MASH) and fibrosis 2/3 (F2/F3) stage of liver fibrosis. In some embodiments, the liver disease is non-cirrhotic non-alcoholic steatohepatitis (NASH) with F2/F3 stage of liver fibrosis. In some embodiments, the liver disease is non-cirrhotic metabolic-associated steatohepatitis (MASH) with F2/F3 stage of liver fibrosis. In some embodiments, the liver disease can be selected
35 from non-alcoholic fatty liver disease (NAFLD) with moderate to advanced liver fibrosis, non-

alcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis, metabolic-associated fatty liver disease (MAFLD) with moderate to advanced liver fibrosis, metabolic-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis, non-alcoholic steatohepatitis with moderate to advanced liver fibrosis, metabolic-associated steatohepatitis with moderate to advanced liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with moderate to advanced liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with moderate to advanced liver fibrosis.

In some embodiments, the liver disease can be selected from non-alcoholic fatty liver disease (NAFLD) with F3 stage of liver fibrosis, non-alcoholic steatohepatitis (NASH) with F3 stage of liver fibrosis, metabolic-associated fatty liver disease (MAFLD) with F3 stage of liver fibrosis, metabolic-associated steatohepatitis (MASH) with F3 stage of liver fibrosis, non-alcoholic steatohepatitis with F3 stage of liver fibrosis, metabolic-associated steatohepatitis with F3 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F3 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F3 stage of liver fibrosis.

In some embodiments, the liver disease is non-cirrhotic non-alcoholic steatohepatitis (NASH) and fibrosis 3 (F3) stage of liver fibrosis. In some embodiments, the liver disease is non-cirrhotic metabolic-associated steatohepatitis (MASH) and fibrosis 3 (F3) stage of liver fibrosis. In some embodiments, the liver disease is non-cirrhotic non-alcoholic steatohepatitis (NASH) with F3 stage of liver fibrosis. In some embodiments, the liver disease is non-cirrhotic metabolic-associated steatohepatitis (MASH) with F3 stage of liver fibrosis. In some embodiments, the liver disease can be selected from non-alcoholic fatty liver disease (NAFLD) with advanced liver fibrosis, non-alcoholic steatohepatitis (NASH) with advanced liver fibrosis, metabolic-associated fatty liver disease (MAFLD) with advanced liver fibrosis, metabolic-associated steatohepatitis (MASH) with advanced liver fibrosis, non-alcoholic steatohepatitis with advanced liver fibrosis, metabolic-associated steatohepatitis with advanced liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis advanced liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with advanced liver fibrosis.

In some embodiments, the liver disease can be selected from non-alcoholic fatty liver disease (NAFLD) with F3/F4 stage of liver fibrosis, non-alcoholic steatohepatitis (NASH) with F3/F4 stage of liver fibrosis, metabolic-associated fatty liver disease (MAFLD) with F3/F4 stage of liver fibrosis, metabolic-associated steatohepatitis (MASH) with F3/F4 stage of liver fibrosis, non-alcoholic steatohepatitis with F3/F4 stage of liver fibrosis, metabolic-associated steatohepatitis with F3/F4 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F3/F4 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F3/F4 stage of liver fibrosis. In some embodiments, the liver disease is non-cirrhotic non-

alcoholic steatohepatitis (NASH) and fibrosis 3/4 (F3/F4) stage of liver fibrosis. In some embodiments, the liver disease is non-cirrhotic metabolic-associated steatohepatitis (MASH) and fibrosis 3/4 (F3/F4) stage of liver fibrosis. In some embodiments, the liver disease is non-cirrhotic non-alcoholic steatohepatitis (NASH) with F3/F4 stage of liver fibrosis. In some

5 embodiments, the liver disease is non-cirrhotic metabolic-associated steatohepatitis (MASH) with F3/F4 stage of liver fibrosis. In some embodiments, the liver disease can be selected from non-alcoholic fatty liver disease (NAFLD) with advanced to severe liver fibrosis, non-alcoholic steatohepatitis (NASH) with advanced to severe liver fibrosis, metabolic-associated fatty liver disease (MAFLD) with advanced to severe liver fibrosis, metabolic-associated

10 steatohepatitis (MASH) with advanced to severe liver fibrosis, non-alcoholic steatohepatitis with advanced to severe liver fibrosis, metabolic-associated steatohepatitis with advanced to severe liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis advanced to severe liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with advanced to severe liver fibrosis.

15 In some embodiments, the liver disease can be selected from non-alcoholic fatty liver disease (NAFLD) with F4 stage of liver fibrosis, non-alcoholic steatohepatitis (NASH) with F4 stage of liver fibrosis, metabolic-associated fatty liver disease (MAFLD) with F4 stage of liver fibrosis, metabolic-associated steatohepatitis (MASH) with F4 stage of liver fibrosis, non-alcoholic steatohepatitis with F4 stage of liver fibrosis, metabolic-associated steatohepatitis

20 with F4 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F4 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F4 stage of liver fibrosis. In some embodiments, the liver disease is non-cirrhotic non-alcoholic steatohepatitis (NASH) and fibrosis 4 (F4) stage of liver fibrosis. In some embodiments, the liver disease is non-cirrhotic metabolic-associated steatohepatitis (MASH) and fibrosis 4 (F4) stage of liver

25 fibrosis. In some embodiments, the liver disease is non-cirrhotic non-alcoholic steatohepatitis (NASH) with F4 stage of liver fibrosis. In some embodiments, the liver disease is non-cirrhotic metabolic-associated steatohepatitis (MASH) with F4 stage of liver fibrosis. In some embodiments, the liver disease can be selected from non-alcoholic fatty liver disease (NAFLD) with severe liver fibrosis, non-alcoholic steatohepatitis (NASH) with severe liver

30 fibrosis, metabolic-associated fatty liver disease (MAFLD) with severe liver fibrosis, metabolic-associated steatohepatitis (MASH) with severe liver fibrosis, non-alcoholic steatohepatitis with severe liver fibrosis, metabolic-associated steatohepatitis with severe liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis severe liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with severe liver fibrosis.

In some embodiments, the liver disease can be NASH diagnosed according to the steatosis-activity-fibrosis (SAF), wherein:

- a) steatosis score is higher or equal to 1,
- b) activity score is A3 or A4, and
- 5 c) fibrosis score is F2 or F3.

In some embodiments, the liver disease can be NASH diagnosed according to the steatosis-activity-fibrosis (SAF), wherein the SAF-based diagnosis is transformed into the following CRN NAS-based diagnosis, wherein:

- a) CRN-steatosis score is higher or equal to 1, CRN-inflammation (CRN-I) score is higher or equal to 1, and CRN-ballooning (CRN-B) score is higher or equal to 1,
- 10 b) NAS score is higher or equal to 5, or [NAS score is higher or equal to 4 and CRN-I is higher or equal to 2 or CRN-B is higher or equal to 2, and
- c) CRN fibrosis score is F2 or F3.

In some embodiments, the liver disease can be NASH diagnosed according to the steatosis-activity-fibrosis (SAF), wherein:

- a) fatty change score is higher or equal to 1 point,
- b) activity score is higher or equal to 2 points, SAF inflammation score is higher or equal to 1 point and SAF ballooning score is higher or equal to 1 point, and
- c) fibrosis score is selected from F1, F2, F3 or F4.

20 In some embodiments, the liver disease can be MASH diagnosed according to the steatosis-activity-fibrosis (SAF), wherein:

- a) steatosis score is higher or equal to 1,
- b) activity score is A3 or A4, and
- c) fibrosis score is F2 or F3.

25 In some embodiments, the liver disease can be MASH diagnosed according to the steatosis-activity-fibrosis (SAF), wherein the SAF-based diagnosis is transformed into the following CRN NAS-based diagnosis, wherein:

- a) CRN-steatosis score is higher or equal to 1, CRN-inflammation (CRN-I) score is higher or equal to 1, and CRN-ballooning (CRN-B) score is higher or equal to 1,
- 30 b) NAS score is higher or equal to 5, or NAS score is higher or equal to 4 and CRN-I is higher or equal to 2 or CRN-B is higher or equal to 2, and
- c) CRN fibrosis score is F2 or F3;

In one embodiment, the liver disease can be MASH diagnosed according to the steatosis-activity-fibrosis (SAF), wherein:

- 35 a) fatty change score is higher or equal to 1 point,

b) activity score is higher or equal to 2 points, SAF inflammation score is higher or equal to 1 point and SAF ballooning score is higher or equal to 1 point, and

c) fibrosis score is selected from F1, F2, F3 or F4.

In some embodiments, the liver disease can be associated with diabetes, and in particular with type 2 diabetes. Examples of liver disease associated with diabetes include: non-alcoholic fatty liver disease (NAFLD) associated with diabetes, non-alcoholic steatohepatitis (NASH) associated with diabetes, metabolic-associated fatty liver disease (MAFLD) associated with diabetes, metabolic-associated steatohepatitis (MASH) associated with diabetes, non-cirrhotic non-alcoholic fatty liver disease (NAFLD) associated with diabetes, non-cirrhotic non-alcoholic steatohepatitis (NASH) associated with diabetes, non-cirrhotic metabolic-associated fatty liver disease (MAFLD) associated with diabetes, non-cirrhotic metabolic-associated steatohepatitis (MASH) associated with diabetes, non-alcoholic steatohepatitis with F0 stage of liver fibrosis associated with diabetes, non-alcoholic steatohepatitis with F0/F1 stage of liver fibrosis associated with diabetes, non-alcoholic steatohepatitis with F1 stage of liver fibrosis associated with diabetes, non-alcoholic steatohepatitis with F1/F2 stage of liver fibrosis associated with diabetes, non-alcoholic steatohepatitis with F2 stage of liver fibrosis associated with diabetes, non-alcoholic steatohepatitis with F2/F3 stage of liver fibrosis associated with diabetes, non-alcoholic steatohepatitis with F3 stage of liver fibrosis associated with diabetes, non-alcoholic steatohepatitis with F3/F4 stage of liver fibrosis associated with diabetes, non-alcoholic steatohepatitis with F4 stage of liver fibrosis associated with diabetes, non-cirrhotic non-alcoholic steatohepatitis with F0 stage of liver fibrosis associated with diabetes, non-cirrhotic non-alcoholic steatohepatitis with F0/F1 stage of liver fibrosis associated with diabetes, non-cirrhotic non-alcoholic steatohepatitis with F1 stage of liver fibrosis associated with diabetes, non-cirrhotic non-alcoholic steatohepatitis with F1/F2 stage of liver fibrosis associated with diabetes, non-cirrhotic non-alcoholic steatohepatitis with F2 stage of liver fibrosis associated with diabetes, non-cirrhotic non-alcoholic steatohepatitis with F2/F3 stage of liver fibrosis associated with diabetes, non-cirrhotic non-alcoholic steatohepatitis with F3 stage of liver fibrosis associated with diabetes, non-cirrhotic non-alcoholic steatohepatitis with F3/F4 stage of liver fibrosis associated with diabetes, non-cirrhotic non-alcoholic steatohepatitis with F4 stage of liver fibrosis associated with diabetes, metabolic-associated steatohepatitis with F0 stage of liver fibrosis associated with diabetes, metabolic-associated steatohepatitis with F0/F1 stage of liver fibrosis associated with diabetes, metabolic-associated steatohepatitis with F1 stage of liver fibrosis associated with diabetes, metabolic-associated steatohepatitis with F1/F2 stage of liver fibrosis associated with diabetes, metabolic-associated

steatohepatitis with F2 stage of liver fibrosis associated with diabetes, metabolic-associated steatohepatitis with F2/F3 stage of liver fibrosis associated with diabetes, metabolic-associated steatohepatitis with F3 stage of liver fibrosis associated with diabetes, metabolic-associated steatohepatitis with F3/F4 stage of liver fibrosis associated with diabetes, 5 metabolic-associated steatohepatitis with F4 stage of liver fibrosis associated with diabetes, non-cirrhotic metabolic-associated steatohepatitis with F0 stage of liver fibrosis associated with diabetes, non-cirrhotic metabolic-associated steatohepatitis with F0/F1 stage of liver fibrosis associated with diabetes, non-cirrhotic metabolic-associated steatohepatitis with F1 stage of liver fibrosis associated with diabetes, non-cirrhotic metabolic-associated steatohepatitis with F1/F2 stage of liver fibrosis associated with diabetes, non-cirrhotic 10 metabolic-associated steatohepatitis with F2 stage of liver fibrosis associated with diabetes, non-cirrhotic metabolic-associated steatohepatitis with F2/F3 stage of liver fibrosis associated with diabetes, non-cirrhotic metabolic-associated steatohepatitis with F3 stage of liver fibrosis associated with diabetes, non-cirrhotic metabolic-associated steatohepatitis with F3/F4 stage of liver fibrosis associated with diabetes, non-cirrhotic metabolic-associated steatohepatitis with F4 stage of liver fibrosis associated with diabetes, the list being not 15 limitative.

In some embodiments, lanifibranor or a deuterated form thereof is formulated in a first pharmaceutical composition and the GLP-1/GIP dual receptor agonist is formulated in a 20 second, distinct, pharmaceutical composition.

As used herein, the term "pharmaceutical composition" indicates a mixture containing ingredients that are compatible when mixed and which may be administered. A pharmaceutical composition may include one or more active principle(s). Additionally, the pharmaceutical composition may include one or more pharmaceutically acceptable 25 excipients, such as carriers, buffers, acidifying agents, alkalizing agents, solvents, adjuvants, tonicity adjusters, emollients, expanders, preservatives, binders, disintegrants, fillers, glidants, lubricants, physical and chemical stabilizers e.g. surfactants, antioxidants and other components, whether these are considered active or inactive principle(s). Such compositions can be prepared by conventional methods, as described e.g. in Remington's Pharmaceutical 30 Sciences, 19th Edition (Mack Publishing Company, 1995), incorporated herein by reference. Pharmaceutical compositions of the present disclosure comprise the lanifibranor or a deuterated form thereof and the GLP-1/GIP dual receptor agonist as active principle(s) and one or more pharmaceutically acceptable excipients. When lanifibranor or a deuterated form thereof and GLP-1/GIP dual receptor agonist are formulated in two distinct pharmaceutical 35 compositions, the first pharmaceutical composition comprises lanifibranor or a deuterated

form thereof as active principle and one or more pharmaceutically acceptable excipients, and the second pharmaceutical composition comprises the GLP-1/GIP dual receptor agonist as active principle and one or more pharmaceutically acceptable excipients. When lanifibranor or a deuterated form thereof and the GLP-1/GIP dual receptor agonist are formulated in the same pharmaceutical composition, the pharmaceutical composition comprises lanifibranor or a deuterated form thereof and the GLP-1/GIP dual receptor agonist as active principles and one or more pharmaceutically acceptable excipients. The choice of excipient(s) will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. In some embodiments, the pharmaceutically acceptable excipients include at least one of a binder, a disintegrant, a filler, a glidant, a lubricant, and a surfactant. In some embodiments, both pharmaceutical compositions can have two identical or different formulations, for example as so-called kit-of-parts. In some embodiments, both pharmaceutical compositions are administered simultaneously. If they are administered simultaneously, lanifibranor or a deuterated form thereof and the GLP-1/GIP dual receptor agonist are given to the patient together, including a few seconds apart.

In some embodiments, lanifibranor or a deuterated form thereof and the GLP-1/GIP dual receptor agonist are administered sequentially, for example a few minutes or a few hours apart. In some embodiments, lanifibranor or a deuterated form thereof and the GLP-1/GIP dual receptor agonist are administered over a period of time, for example lanifibranor or a deuterated form thereof is administered first and the GLP-1/GIP dual receptor agonist is administered a few days after administration of lanifibranor.

In some embodiments, lanifibranor or a deuterated form thereof and the GLP-1/GIP dual receptor agonist are formulated in the same pharmaceutical composition. Suitable pharmaceutical compositions include pharmaceutical compositions for administration by the oral, parenteral (such as intramuscular, intravenous, intradermal or subcutaneous), rectal, or topical route. Advantageously, such pharmaceutical compositions are unit dosage forms suitable for the single administration of the desired amount of active principle. In such form, pharmaceutical compositions are divided into unit doses containing appropriate quantities of the active principles. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparations, for example, a solid dosage form. In some embodiments, the pharmaceutical composition is a solid dosage form. Exemplary solid dosage forms include tablets, capsules, stick-packs, sachets, lozenges, powders, pills, or granules. Preferred solid dosage forms include tablets, capsules and stick-packs, tablets being especially preferred. In some embodiments, the pharmaceutical composition is an

injectable. In some embodiments, the pharmaceutical composition may be provided together with a device for application, for example together with a syringe, an injection pen or an autoinjector. Such devices may be provided separate from a pharmaceutical composition or prefilled with the pharmaceutical composition.

- 5 In some embodiments, pharmaceutical compositions containing lanifibranor (or a deuterated form thereof) are pharmaceutical compositions for oral administration, as defined above. Such pharmaceutical compositions advantageously comprise from about 0.5 mg to about 1,200 mg of lanifibranor (or a deuterated form thereof). Exemplary pharmaceutical compositions comprise at least 0.5 mg, at least 1 mg, at least 2 mg, at least 3 mg, at least 4
10 mg, at least 5 mg, at least 10 mg, at least 15 mg, at least 20 mg, at least 25 mg, at least 30 mg, at least 35 mg, at least 40 mg, at least 45 mg, at least 50 mg, at least 55 mg, at least 60 mg, at least 65 mg, at least 70 mg, at least 75 mg, at least 80 mg, at least 85 mg, at least 90 mg, at least 95 mg, at least 100 mg, at least 150 mg, at least 200 mg, at least 250 mg, at least 300 mg, at least 350 mg, at least 400 mg, at least 450 mg, at least 500 mg, at
15 least 550 mg, at least 600 mg, at least 650 mg, at least 700 mg, at least 750 mg, at least 800 mg, at least 850 mg, at least 900 mg, at least 950 mg, at least 1,000 mg, at least 1,050 mg, at least 1,100 mg, at least 1,150 mg, or 1,200 mg of lanifibranor (or a deuterated form thereof).

Exemplary pharmaceutical compositions comprise 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg,
20 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 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, 1,050 mg, 1,100 mg, 1,150 mg, or 1,200 mg of lanifibranor (or a deuterated form thereof).

- 25 Lanifibranor (or a deuterated form thereof) can be administered once daily ("QD"), twice daily ("BID"), three times daily ("TID") or four times daily ("QID") provided the daily dose does not exceed 1,200 mg.

In some embodiments, lanifibranor (or a deuterated form thereof) is administered to a subject with a meal. In some embodiments, lanifibranor (or a deuterated form thereof) is
30 administered to a subject under fasted conditions.

In some embodiments, pharmaceutical compositions containing a GLP-1/GIP dual receptor agonist are pharmaceutical compositions for parenteral administration (for example subcutaneous, intramuscular, intradermal or intravenous), as defined above. In some
35 embodiments, pharmaceutical compositions containing a GLP-1/GIP dual receptor agonist are pharmaceutical compositions for subcutaneous route. Such pharmaceutical compositions

comprise from about 0.01 mg to about 100 mg of said agonist. Exemplary pharmaceutical compositions comprise at least 0.01 mg, at least 0.02 mg, at least 0.03 mg, at least 0.04 mg, at least 0.05 mg, at least 0.06 mg, at least 0.07 mg, at least 0.08 mg, at least 0.09 mg, at least 0.10 mg, at least 0.15 mg, at least 0.20 mg, at least 0.25 mg, at least 0.30 mg, at least 0.35 mg, at least 0.40 mg, at least 0.45 mg, at least 0.50 mg, at least 0.55 mg, at least 0.60 mg, at least 0.65 mg, at least 0.70 mg, at least 0.75 mg, at least 0.80 mg, at least 0.85 mg, at least 0.90 mg, at least 0.95 mg, at least 1.0 mg, at least 1.5 mg, at least 1.8 mg, at least 2.0 mg, at least 2.4 mg, at least 2.5 mg, at least 3.0 mg, at least 3.5 mg, at least 3.6 mg, at least 4.0 mg, at least 4.5 mg, at least 4.8 mg, at least 5.0 mg, at least 5.5 mg, at least 6.0 mg, at least 6.5 mg, at least 7.0 mg, at least 7.5 mg, at least 8.0 mg, at least 8.5 mg, at least 9.0 mg, at least 9.5 mg, at least 10.0 mg, at least 10.5 mg, at least 11.0 mg, at least 11.5 mg, at least 12.0 mg, at least 12.5 mg, at least 13.0 mg, at least 13.5 mg, at least 14.0 mg, at least 14.5 mg, at least 15.0 mg, at least 15.5 mg, at least 16.0 mg, at least 16.5 mg, at least 17.0 mg, at least 17.5 mg, at least 18.0 mg, at least 18.5 mg, at least 19.0 mg, at least 19.5 mg, at least 20.0 mg, at least 20.5 mg, at least 21.0 mg, at least 21.5 mg, at least 22.0 mg, at least 22.5 mg, at least 23.0 mg, at least 23.5 mg, at least 24.0 mg, at least 24.5 mg, at least 25.0 mg, at least 25.5 mg, at least 26.0 mg, at least 26.5 mg, at least 27.0 mg, at least 27.5 mg, at least 28.0 mg, at least 28.5 mg, at least 29.0 mg, at least 29.5 mg, at least 30.0 mg, at least 30.5 mg, at least 31.0 mg, at least 31.5 mg, at least 32.0 mg, at least 32.5 mg, at least 33.0 mg, at least 33.5 mg, at least 34.0 mg, at least 34.5 mg, at least 35.0 mg, at least 40.0 mg, at least 45.0 mg, at least 50.0 mg, at least 50.5 mg, at least 51.0 mg, at least 51.5 mg, at least 52.0 mg, at least 52.5 mg, at least 53.0 mg, at least 53.5 mg, at least 54.0 mg, at least 54.5 mg, at least 55.0 mg, at least 55.5 mg, at least 56.0 mg, at least 56.5 mg, at least 57.0 mg, at least 57.5 mg, at least 58.0 mg, at least 58.5 mg, at least 59.0 mg, at least 59.5 mg, at least 60.0 mg, at least 60.5 mg, at least 61.0 mg, at least 61.5 mg, at least 62.0 mg, at least 62.5 mg, at least 63.0 mg, at least 63.5 mg, at least 64.0 mg, at least 64.5 mg, at least 65.0 mg, at least 65.5 mg, at least 66.0 mg, at least 66.5 mg, at least 67.0 mg, at least 67.5 mg, at least 68.0 mg, at least 68.5 mg, at least 69.0 mg, at least 69.5 mg, at least 70.0 mg, at least 70.5 mg, at least 71.0 mg, at least 71.5 mg, at least 72.0 mg, at least 72.5 mg, at least 73.0 mg, at least 73.5 mg, at least 74.0 mg, at least 74.5 mg, at least 75.0 mg, at least 75.5 mg, at least 76.0 mg, at least 76.5 mg, at least 77.0 mg, at least 77.5 mg, at least 78.0 mg, at least 78.5 mg, at least 79.0 mg, at least 79.5 mg, at least 80.0 mg, at least 80.5 mg, at least 81.0 mg, at least 81.5 mg, at least 82.0 mg, at least 82.5 mg, at least 83.0 mg, at least 83.5 mg, at least 84.0 mg, at least 84.5 mg, at least 85.0 mg, at least 85.5 mg, at least 86.0 mg, at least 86.5 mg, at least 87.0 mg, at least 87.5 mg, at least

88.0 mg, at least 88.5 mg, at least 89.0 mg, at least 89.5 mg, at least 90.0 mg, at least 90.5 mg, at least 91.0 mg, at least 91.5 mg, at least 92.0 mg, at least 92.5 mg, at least 93.0 mg, at least 93.5 mg, at least 94.0 mg, at least 94.5 mg, at least 95.0 mg, at least 95.5 mg, at least 96.0 mg, at least 96.5 mg, at least 97.0 mg, at least 97.5 mg, at least 98.0 mg, at least 98.5 mg, at least 99.0 mg, at least 99.5 mg, or 100.0 mg of GLP-1/GIP dual receptor agonist.

Exemplary pharmaceutical compositions comprise 0.01 mg, 0.02 mg, 0.03 mg, 0.04 mg, 0.05 mg, 0.06 mg, 0.07 mg, 0.08 mg, 0.09 mg, 0.10 mg, 0.15 mg, 0.20 mg, 0.25 mg, 0.30 mg, 0.35 mg, 0.40 mg, 0.45 mg, 0.50 mg, 0.55 mg, 0.60 mg, 0.65 mg, 0.70 mg, 0.75 mg, 0.80 mg, 0.85 mg, 0.90 mg, 0.95 mg, 1.0 mg, 1.5 mg, 1.8 mg, 2.0 mg, 2.4 mg, 2.5 mg, 3.0 mg, 3.5 mg, 3.6 mg, 4.0 mg, 4.5 mg, 4.8 mg, 5.0 mg, 5.5 mg, 6.0 mg, 6.5 mg, 7.0 mg, 7.5 mg, 8.0 mg, 8.5 mg, 9.0 mg, 9.5 mg, 10.0 mg, 10.5 mg, 11.0 mg, 11.5 mg, 12.0 mg, 12.5 mg, 13.0 mg, 13.5 mg, 14.0 mg, 14.5 mg, 15.0 mg, 15.5 mg, 16.0 mg, 16.5 mg, 17.0 mg, 17.5 mg, 18.0 mg, 18.5 mg, 19.0 mg, 19.5 mg, 20.0 mg, 20.5 mg, 21.0 mg, 21.5 mg, 22.0 mg, 22.5 mg, 23.0 mg, 23.5 mg, 24.0 mg, 24.5 mg, 25.0 mg, 25.5 mg, 26.0 mg, 26.5 mg, 27.0 mg, 27.5 mg, 28.0 mg, 28.5 mg, 29.0 mg, 29.5 mg, 30.0 mg, 30.5 mg, 31.0 mg, 31.5 mg, 32.0 mg, 32.5 mg, 33.0 mg, 33.5 mg, 34.0 mg, 34.5 mg, 35.0 mg, 35.5 mg, 36.0 mg, 36.5 mg, 37.0 mg, 37.5 mg, 38.0 mg, 38.5 mg, 39.0 mg, 39.5 mg, 40.0 mg, 40.5 mg, 41.0 mg, 41.5 mg, 42.0 mg, 42.5 mg, 43.0 mg, 43.5 mg, 44.0 mg, 44.5 mg, 45.0 mg, 45.5 mg, 46.0 mg, 46.5 mg, 47.0 mg, 47.5 mg, 48.0 mg, 48.5 mg, 49.0 mg, 49.5 mg, 50.0 mg, 50.5 mg, 51.0 mg, 51.5 mg, 52.0 mg, 52.5 mg, 53.0 mg, 53.5 mg, 54.0 mg, 54.5 mg, 55.0 mg, 55.5 mg, 56.0 mg, 56.5 mg, 57.0 mg, 57.5 mg, 58.0 mg, 58.5 mg, 59.0 mg, 59.5 mg, 60.0 mg, 60.5 mg, 61.0 mg, 61.5 mg, 62.0 mg, 62.5 mg, 63.0 mg, 63.5 mg, 64.0 mg, 64.5 mg, 65.0 mg, 65.5 mg, 66.0 mg, 66.5 mg, 67.0 mg, 67.5 mg, 68.0 mg, 68.5 mg, 69.0 mg, 69.5 mg, 70.0 mg, 70.5 mg, 71.0 mg, 71.5 mg, 72.0 mg, 72.5 mg, 73.0 mg, 73.5 mg, 74.0 mg, 74.5 mg, 75.0 mg, 75.5 mg, 76.0 mg, 76.5 mg, 77.0 mg, 77.5 mg, 78.0 mg, 78.5 mg, 79.0 mg, 79.5 mg, 80.0 mg, 80.5 mg, 81.0 mg, 81.5 mg, 82.0 mg, 82.5 mg, 83.0 mg, 83.5 mg, 84.0 mg, 84.5 mg, 85.0 mg, 85.5 mg, 86.0 mg, 86.5 mg, 87.0 mg, 87.5 mg, 88.0 mg, 88.5 mg, 89.0 mg, 89.5 mg, 90.0 mg, 90.5 mg, 91.0 mg, 91.5 mg, 92.0 mg, 92.5 mg, 93.0 mg, 93.5 mg, 94.0 mg, 94.5 mg, 95.0 mg, 95.5 mg, 96.0 mg, 96.5 mg, 97.0 mg, 97.5 mg, 98.0 mg, 98.5 mg, 99.0 mg, 99.5 mg, or 100.0 mg of said agonist.

The GLP-1/GIP dual receptor agonist can be administered once daily, twice weekly, once weekly, once bi-weekly, once monthly or once bi-monthly.

In embodiments where lanifibranor (or a deuterated form thereof) and the GLP-1/GIP dual receptor agonist are present in the same pharmaceutical composition, each active principle can be present in the respective amounts indicated above.

When lanifibranor or a deuterated form thereof and the GLP-1/GIP dual receptor agonist are formulated in the same pharmaceutical composition, said pharmaceutical composition comprises from about 0.5 mg to about 1,200 mg of lanifibranor or a deuterated form thereof, and from about 0.01 mg to about 100.0 mg of GLP-1/GIP dual receptor agonist and at least one pharmaceutically acceptable excipient as described above.

In some embodiments, the product further comprises at least one additional active pharmaceutical ingredient, such as for example an ACC inhibitor (e.g. firsocostat), an anti-diabetic agent, including but not limited to a biguanide (e.g. metformin), a sulfonylurea, a meglitinide or glinide (e.g. nateglinide), a DPP-IV inhibitor, a GLP-1 receptor agonist (which is different from the compounds of the invention), an inhibitor of the sodium glucose co-transporter-2 (SGLT-2), a GPR40 agonist (FFAR1/FFA1 agonist, e.g. fasiglifam), an insulin or an insulin analogue (e.g. a compound that mimics at least one effect of insulin), a FXR agonist, an endothelin receptor antagonist, a glucose-dependent insulinotropic polypeptide (GIP) agonist, a GPR40 agonist, a FFAR1/FFA1 agonist (such as fasiglifam), an insulin or an insulin analogue (e.g. a compound that mimics at least one effect of insulin), an activator of the fibroblast growth factor receptor 1c-beta-klotho (FGFR1c/KLB) pathway (e.g. efruxifermin and NGM313), or a FGF19 analogue (such as aldafermin).

Examples of SGLT2 inhibitors include Invokana / Canagliflozin, Forxiga / Dapagliflozin, Remogliflozin, Sergliflozin, Empagliflozin, Ipragliflozin, Tofogliflozin, Luseogliflozin, Sotagliflozin (LX-4211), Ertugliflozin / PF-04971729, RO-4998452, Bexagliflozin (EGT-0001442), KGA-3235 / DSP-3235, LIK066, SBM-TFC-039, Henagliflozin (SHR3824), Janagliflozin, Tianagliflozin, AST1935, JRP493, HEC-44616, the list being not limitative.

Examples of DPP-IV (also referred to as DDP-4 or dipeptidylpeptidase IV) inhibitors, for example: alogliptin / Nesina, Trajenta / linagliptin / BI-1356 / Ondero / Trajenta / Tradjenta / Trayenta / Tradzenta, saxagliptin / Onglyza, sitagliptin / Januvia / Xelevia / Tesave / Janumet / Velmetia, Galvus / vildagliptin, anagliptin, gemigliptin, teneligliptin, melogliptin, trelagliptin, DA- 1229, omarigliptin / MK-3102, KM-223, evogliptin, ARI-2243, PBL-1427, pinoxacin, the list being not limitative.

Examples of GLP-1 receptor agonists include GLP-1 and GLP-1 analogues, exendin-4 and exendin-4 analogues, semaglutide, liraglutide (Saxenda[®], Victoza[®]), exenatide (Byetta[®] and Bydureon[®]), Byetta LAR[®], lixisenatide (Lyxumia[®]), Dulaglutide and Albiglutide.

Examples of insulin analogues include, but are not limited to, Lantus®, Novorapid®, Humalog®, Novomix®, Actraphane® HM, Levemir® Degludec® and Apidra®, the list being not limitative.

5 Examples of FXR agonists (also called Farnesoid X Receptor agonist) include without being limitative, obeticholic acid (OCA), cilofexor (GS-9674), tropifexor (LJN-452), vonafexor (EYP001), nidufexor (LMB763), MET-409, TERN-101 (LY2562175), PX-104, AKN-083, GNF-5120, INV-33, NTX-023-1, INT-787, lithocholic acid (LCA), deoxycholic acid (DCA), chenodeoxycholic acid (CDCA), EP-024297, Px-103, SR-45023 and EDP-305®, the list being not limitative.

10 The use of the product according to the invention, or a physiologically acceptable salt thereof, in combination with one or more active pharmaceutical ingredient may take place simultaneously, separately or sequentially.

The use of the product according to the invention, or a physiologically acceptable salt thereof, in combination with another active pharmaceutical ingredient may take place
15 simultaneously or at staggered times, but particularly within a short space of time. If they are administered simultaneously, the two active substances are given to the patient together; if they are used at staggered times, the two active substances are given to the patient within a period of less than or equal to 12 hours, but particularly less than or equal to 6 hours.

20 Consequently, in another aspect, this invention relates to a medicament which comprises a product according to the invention or a physiologically acceptable salt of such a product and at least one of the active pharmaceutical ingredients described above as combination partners, optionally together with one or more pharmaceutical excipients.

The product according to the invention, or physiologically acceptable salt or solvate thereof,
25 and the additional active pharmaceutical ingredient to be combined therewith may both be present together in one formulation, for example a tablet or capsule, or separately in two identical or different formulations, for example as so-called kit-of-parts.

In another aspect, the present disclosure provides a combination of (i) lanifibranor or a deuterated form thereof and (ii) a GLP-1/GIP dual receptor agonist for use as a medicament.

30 In another aspect, the present disclosure provides a combination of (i) lanifibranor or a deuterated form thereof and (ii) a GLP-1/GIP dual receptor agonist for use in the prevention and/or the treatment of a liver disease. In some embodiments, the combination further comprises at least one additional active pharmaceutical ingredient as defined above.

In another aspect, the present disclosure provides a method of preventing and/or treating a
35 liver disease, which comprises administering to a subject in need thereof (i) an effective

amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

According to embodiments that involve administering to a patient in need of treatment an "effective amount", "therapeutically effective" or "an amount effective to treat" or

5 "pharmaceutically effective" denotes the amount of lanifibranor, or a deuterated form thereof and of GLP-1/GIP dual receptor agonist needed to inhibit or reverse a disease condition (e.g., to treat liver disease). Determining an effective amount specifically depends on such factors as toxicity and efficacy of the medicament. These factors will differ depending on other factors such as potency, relative bioavailability, patient body weight, 10 severity of adverse side-effects and preferred mode of administration. Toxicity may be determined using methods well known in the art. Efficacy may be determined utilizing the same guidance. An effective amount, therefore, is an amount that is deemed by the clinician to be toxicologically tolerable, yet efficacious. This amount can be a fixed dose for all subjects being treated, or can vary depending upon the physical condition of the subject to 15 be treated, a professional assessment of the medical situation, and other relevant factors.

In some embodiments, the method further comprises administering to the subject an effective amount of at least one additional active pharmaceutical ingredient as defined above.

In another aspect, the present disclosure provides a method of preventing a liver disease in 20 a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the method further comprises administering to the subject an effective amount of at least one additional active pharmaceutical ingredient as defined above.

In another aspect, the present disclosure provides a method of preventing a liver disease in 25 a subject under treatment with a GLP-1/GIP dual receptor agonist, which comprises administering to the subject an effective amount of lanifibranor or a deuterated form thereof. In some embodiments, the method further comprises administering to the subject an effective amount of at least one additional active pharmaceutical ingredient as defined above.

30 In another aspect, the present disclosure provides the use of lanifibranor, or a deuterated form thereof, and a GLP-1/GIP dual receptor agonist in the manufacture of a medicament intended for the prevention of a liver disease.

In the context of the present disclosure, the various embodiments disclosed in relation to the first aspect disclosed herein also apply to the other aspects described herein.

In some embodiments, the present disclosure relates to a method of preventing cirrhosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

- 5 In some embodiments, the present disclosure relates to a method of preventing cirrhosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of preventing liver fibrosis, which comprises administering to a subject in need thereof (i) an effective amount of
10 lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of preventing liver fibrosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

- 15 In some embodiments, the present disclosure relates to a method of preventing liver steatosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of preventing liver
20 steatosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of preventing fatty liver disease, which comprises administering to a subject in need thereof (i) an effective amount
25 of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of preventing fatty liver disease in a subject under treatment lanifibranor or a deuterated form thereof, which
30 comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of preventing acute decompensation or acute decompensation of cirrhosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of preventing acute decompensation or acute decompensation of cirrhosis in a subject under treatment lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

- 5 In some embodiments, the present disclosure relates to a method of preventing acute decompensation of cirrhosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of preventing acute
10 decompensation of cirrhosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of preventing acute-on-chronic liver failure, which comprises administering to a subject in need thereof (i) an
15 effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of preventing acute-on-chronic liver failure in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP
20 dual receptor agonist.

In some embodiments, the present disclosure relates to a method of preventing acute liver failure, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

- 25 In some embodiments, the present disclosure relates to a method of preventing acute liver failure in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of preventing
30 decompensated cirrhosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of preventing decompensated cirrhosis in a subject under treatment with lanifibranor or a deuterated form

thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of preventing compensated cirrhosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of preventing compensated cirrhosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of preventing non-alcoholic fatty liver disease, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of preventing non-alcoholic fatty liver disease in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of preventing non-alcoholic steatohepatitis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of preventing non-alcoholic steatohepatitis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of preventing metabolic-associated fatty liver disease, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of preventing metabolic-associated fatty liver disease in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of preventing metabolic-associated steatohepatitis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

- 5 In some embodiments, the present disclosure relates to a method of preventing metabolic-associated steatohepatitis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

- 10 In some embodiments, the present disclosure relates to a method of preventing autoimmune cholangitis which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

- 15 In some embodiments, the present disclosure relates to a method of preventing autoimmune cholangitis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

- 20 In some embodiments, the present disclosure relates to a method of preventing primary biliary cholangitis which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

- In some embodiments, the present disclosure relates to a method of preventing primary biliary cholangitis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

- 25 In some embodiments, the present disclosure relates to a method of preventing primary sclerosing cholangitis which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

- 30 In some embodiments, the present disclosure relates to a method of preventing primary sclerosing cholangitis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of preventing autoimmune cholangiopathy which comprises administering to a subject in need thereof (i) an effective

amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of preventing autoimmune cholangiopathy in a subject under treatment with lanifibranor or a deuterated form thereof,
5 which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of preventing hepatocarcinoma which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.
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In some embodiments, the present disclosure relates to a method of preventing hepatocarcinoma in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

15 In some embodiments, the present disclosure relates to a method of preventing liver cirrhosis which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of preventing liver
20 cirrhosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of preventing non-cirrhotic non-alcoholic steatohepatitis with F0 stage of fibrosis, which comprises administering to a
25 subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of preventing non-cirrhotic non-alcoholic steatohepatitis with F0/F1 stage of fibrosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of preventing non-cirrhotic non-alcoholic steatohepatitis with F1 stage of fibrosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a
30 method of preventing non-cirrhotic non-alcoholic steatohepatitis with F1/F2 stage of fibrosis,
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which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of preventing non-cirrhotic non-alcoholic steatohepatitis with F2 stage of fibrosis, which

5 comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of preventing non-cirrhotic non-alcoholic steatohepatitis with F2/F3 stage of fibrosis, which comprises

10 administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of preventing non-cirrhotic non-alcoholic steatohepatitis with F3 stage of fibrosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments,

15 the present disclosure relates to a method of preventing non-cirrhotic non-alcoholic steatohepatitis with F3/F4 stage of fibrosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of preventing non-cirrhotic non-alcoholic steatohepatitis with

20 F4 stage of fibrosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of preventing non-cirrhotic non-alcoholic steatohepatitis with F0 stage of fibrosis in a subject under treatment with

25 lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of preventing non-cirrhotic non-alcoholic steatohepatitis with F0/F1 stage of fibrosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP

30 dual receptor agonist. In some embodiments, the present disclosure relates to a method of preventing non-cirrhotic non-alcoholic steatohepatitis with F1 stage of fibrosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of preventing non-cirrhotic

35 non-alcoholic steatohepatitis with F1/F2 stage of fibrosis in a subject under treatment with

lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of preventing non-cirrhotic non-alcoholic steatohepatitis with F2 stage of fibrosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of preventing non-cirrhotic non-alcoholic steatohepatitis with F2/F3 stage of fibrosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of preventing non-cirrhotic non-alcoholic steatohepatitis with F3 stage of fibrosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of preventing non-cirrhotic non-alcoholic steatohepatitis with F3/F4 stage of fibrosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of preventing non-cirrhotic non-alcoholic steatohepatitis with F4 stage of fibrosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of preventing non-cirrhotic metabolic-associated steatohepatitis with F0 stage of fibrosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of preventing non-cirrhotic metabolic-associated steatohepatitis with F0/F1 stage of fibrosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of preventing non-cirrhotic metabolic-associated steatohepatitis with F1 stage of fibrosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of preventing non-cirrhotic metabolic-associated steatohepatitis with F1/F2 stage of fibrosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a

deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of preventing non-cirrhotic metabolic-associated steatohepatitis with F2 stage of fibrosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist. In some

5 embodiments, the present disclosure relates to a method of preventing non-cirrhotic metabolic-associated steatohepatitis with F2/F3 stage of fibrosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

10 In some embodiments, the present disclosure relates to a method of preventing non-cirrhotic metabolic-associated steatohepatitis with F3 stage of fibrosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist. In some

15 embodiments, the present disclosure relates to a method of preventing non-cirrhotic metabolic-associated steatohepatitis with F3/F4 stage of fibrosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist. In some

20 embodiments, the present disclosure relates to a method of preventing non-cirrhotic metabolic-associated steatohepatitis with F4 stage of fibrosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

 In some embodiments, the present disclosure relates to a method of preventing non-cirrhotic metabolic-associated steatohepatitis with F0 stage of fibrosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject

25 an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of preventing non-cirrhotic metabolic-associated steatohepatitis with F0/F1 stage of fibrosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist. In some

30 embodiments, the present disclosure relates to a method of preventing non-cirrhotic metabolic-associated steatohepatitis with F1 stage of fibrosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist. In some

35 embodiments, the present disclosure relates to a method of preventing non-cirrhotic metabolic-associated steatohepatitis with F1/F2 stage of fibrosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises

administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of preventing non-cirrhotic metabolic-associated steatohepatitis with F2 stage of fibrosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject

5 an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of preventing non-cirrhotic metabolic-associated steatohepatitis with F2/F3 stage of fibrosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount

10 of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of preventing non-cirrhotic metabolic-associated steatohepatitis with F3 stage of fibrosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of preventing non-cirrhotic metabolic-associated steatohepatitis with F3/F4 stage of fibrosis in a subject

15 under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of preventing non-cirrhotic metabolic-associated steatohepatitis with F4 stage of fibrosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject

20 an effective amount of a GLP-1/GIP dual receptor agonist.

In another aspect, the present disclosure provides a method of treating a liver disease in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the method further comprises administering to the subject an effective

25 amount of at least one additional active pharmaceutical ingredient as defined above.

In another aspect, the present disclosure provides a method of treating a liver disease in a subject under treatment with a GLP-1/GIP dual receptor agonist, which comprises administering to the subject an effective amount of lanifibranor or a deuterated form thereof. In some embodiments, the method further comprises administering to the subject an

30 effective amount of at least one additional active pharmaceutical ingredient as defined above.

In another aspect, the present disclosure provides the use of lanifibranor, or a deuterated form thereof, and a GLP-1/GIP dual receptor agonist in the manufacture of a medicament intended for the treatment of a liver disease.

In the context of the present disclosure, the various embodiments disclosed in relation to the first aspect disclosed herein also apply to the other aspects described herein.

In some embodiments, the present disclosure relates to a method of treating cirrhosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of treating cirrhosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

10 In some embodiments, the present disclosure relates to a method of treating liver fibrosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

15 In some embodiments, the present disclosure relates to a method of treating liver fibrosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of treating liver steatosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a
20 GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of treating liver steatosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

25 In some embodiments, the present disclosure relates to a method of treating fatty liver disease, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of treating fatty liver disease in a subject under treatment with lanifibranor or a deuterated form thereof, which
30 comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of treating acute decompensation, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-
35 1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of treating acute decompensation in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

- 5 In some embodiments, the present disclosure relates to a method of treating acute decompensation of cirrhosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

10 In some embodiments, the present disclosure relates to a method of treating acute decompensation of cirrhosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

15 In some embodiments, the present disclosure relates to a method of treating acute-on-chronic liver failure, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

20 In some embodiments, the present disclosure relates to a method of treating acute-on-chronic liver failure in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of treating acute liver failure, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

- 25 In some embodiments, the present disclosure relates to a method of treating acute liver failure in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

30 In some embodiments, the present disclosure relates to a method of treating decompensated cirrhosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of treating decompensated cirrhosis in a subject under treatment with lanifibranor or a deuterated form

thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of treating compensated cirrhosis, which comprises administering to a subject in need thereof (i) an effective amount
5 of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of treating compensated cirrhosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor
10 agonist.

In some embodiments, the present disclosure relates to a method of treating non-alcoholic fatty liver disease, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

15 In some embodiments, the present disclosure relates to a method of treating non-alcoholic fatty liver disease in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of treating non-alcoholic
20 steatohepatitis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of treating non-alcoholic steatohepatitis in a subject under treatment with lanifibranor or a deuterated form thereof,
25 which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of treating metabolic-associated fatty liver disease, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount
30 of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of treating metabolic-associated fatty liver disease in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of treating metabolic-associated steatohepatitis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

- 5 In some embodiments, the present disclosure relates to a method of treating metabolic-associated steatohepatitis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

- 10 In some embodiments, the present disclosure relates to a method of treating autoimmune cholangitis which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

- 15 In some embodiments, the present disclosure relates to a method of treating autoimmune cholangitis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

- 20 In some embodiments, the present disclosure relates to a method of treating primary biliary cholangitis which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

- In some embodiments, the present disclosure relates to a method of treating primary biliary cholangitis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

- 25 In some embodiments, the present disclosure relates to a method of treating primary sclerosing cholangitis which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

- 30 In some embodiments, the present disclosure relates to a method of treating primary sclerosing cholangitis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of treating autoimmune cholangiopathy which comprises administering to a subject in need thereof (i) an effective

amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of treating autoimmune cholangiopathy in a subject under treatment with lanifibranor or a deuterated form thereof,
5 which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of treating hepatocarcinoma which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.
10

In some embodiments, the present disclosure relates to a method of treating hepatocarcinoma in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

15 In some embodiments, the present disclosure relates to a method of treating liver cirrhosis which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of treating liver cirrhosis in
20 a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of treating non-cirrhotic non-alcoholic steatohepatitis with F0 stage of fibrosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof
25 and (ii) an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of treating non-cirrhotic non-alcoholic steatohepatitis with F0/F1 stage of fibrosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present
30 disclosure relates to a method of treating non-cirrhotic non-alcoholic steatohepatitis with F1 stage of fibrosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of treating non-cirrhotic non-alcoholic steatohepatitis with F1/F2 stage of fibrosis,
35 which comprises administering to a subject in need thereof (i) an effective amount of

lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of treating non-cirrhotic non-alcoholic steatohepatitis with F2 stage of fibrosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of treating non-cirrhotic non-alcoholic steatohepatitis with F2/F3 stage of fibrosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of treating non-cirrhotic non-alcoholic steatohepatitis with F3 stage of fibrosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of treating non-cirrhotic non-alcoholic steatohepatitis with F3/F4 stage of fibrosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of treating non-cirrhotic non-alcoholic steatohepatitis with F4 stage of fibrosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

In some embodiments, the present disclosure relates to a method of treating non-cirrhotic non-alcoholic steatohepatitis with F0 stage of fibrosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of treating non-cirrhotic non-alcoholic steatohepatitis with F0/F1 stage of fibrosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of treating non-cirrhotic non-alcoholic steatohepatitis with F1 stage of fibrosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of treating non-cirrhotic non-alcoholic steatohepatitis with F1/F2 stage of fibrosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an

effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of treating non-cirrhotic non-alcoholic steatohepatitis with F2 stage of fibrosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of treating non-cirrhotic non-alcoholic steatohepatitis with F2/F3 stage of fibrosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of treating non-cirrhotic non-alcoholic steatohepatitis with F3 stage of fibrosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of treating non-cirrhotic non-alcoholic steatohepatitis with F3/F4 stage of fibrosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of treating non-cirrhotic non-alcoholic steatohepatitis with F4 stage of fibrosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of treating non-cirrhotic metabolic-associated steatohepatitis with F0 stage of fibrosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of treating non-cirrhotic metabolic-associated steatohepatitis with F0/F1 stage of fibrosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of treating non-cirrhotic metabolic-associated steatohepatitis with F1 stage of fibrosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of treating non-cirrhotic metabolic-associated steatohepatitis with F1/F2 stage of fibrosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates

to a method of treating non-cirrhotic metabolic-associated steatohepatitis with F2 stage of fibrosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of

5 treating non-cirrhotic metabolic-associated steatohepatitis with F2/F3 stage of fibrosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of treating non-

10 cirrhotic metabolic-associated steatohepatitis with F3 stage of fibrosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of treating non-cirrhotic metabolic-associated steatohepatitis with F3/F4 stage of fibrosis, which comprises

15 administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of treating non-cirrhotic metabolic-associated steatohepatitis with F4 stage of fibrosis, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.

20 In some embodiments, the present disclosure relates to a method of treating non-cirrhotic metabolic-associated steatohepatitis with F0 stage of fibrosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of treating non-cirrhotic metabolic-associated

25 steatohepatitis with F0/F1 stage of fibrosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of treating non-cirrhotic metabolic-associated steatohepatitis with F1 stage of fibrosis in a subject under treatment with lanifibranor or a deuterated form thereof, which

30 comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of treating non-cirrhotic metabolic-associated steatohepatitis with F1/F2 stage of fibrosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist. In some

35 embodiments, the present disclosure relates to a method of treating non-cirrhotic metabolic-

associated steatohepatitis with F2 stage of fibrosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of treating non-cirrhotic metabolic-associated steatohepatitis with F2/F3 stage of fibrosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of treating non-cirrhotic metabolic-associated steatohepatitis with F3 stage of fibrosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of treating non-cirrhotic metabolic-associated steatohepatitis with F3/F4 stage of fibrosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist. In some embodiments, the present disclosure relates to a method of treating non-cirrhotic metabolic-associated steatohepatitis with F4 stage of fibrosis in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

Example

C57BL6/J Mice were fed for two weeks with a 60% high fat / 1.25% cholesterol / 0.5% cholic acid diet with 2% 2-hydroxypropyl beta-cyclodextrin in drinking water (HFCC/CDX diet). After 2 weeks of diet, blood was collected (~150µL/heparin) in non-fasting conditions and plasma ALT and AST levels were measured. Mice were then randomized into 9 homogenous treatment groups (n=10 mice per group). The 9 groups received then their treatment for the remaining 2 weeks on top of the HFCC/CDX diet as follows:

- Group 1: vehicle;
- Group 2: lanifibranor 10 mg/kg;
- Group 3: lanifibranor 30 mg/kg;
- Group 4: tirzepatide 3 nmol/kg;
- Group 5: tirzepatide 10 nmol/kg;
- Group 6: lanifibranor 10 mg/kg + tirzepatide 3 nmol/kg;
- Group 7: lanifibranor 30 mg/kg + tirzepatide 3 nmol/kg;
- Group 8: lanifibranor 10 mg/kg + tirzepatide 10 nmol/kg;
- Group 9: lanifibranor 30 mg/kg + tirzepatide 10 nmol/kg.

Treatments with lanifibranor were given QD per os. Treatments with tirzepatide were given QD by subcutaneous injection. Vehicle 1 stands for lanifibranor's vehicle (i.e. methyl cellulose/poloxamer), vehicle 2 stands for tirzepatide's vehicle (i.e. Tween®80/sodium phosphate/sodium chloride). At the end of the treatment period, all the mice were weighted and 4-hour fasted prior to blood collection (maximal volume/EDTA). Plasma was isolated and stored at -80°C prior to assay plasma ALT/AST levels. After blood collection, mice were sacrificed. The liver was collected and weighted then liver samples were dissected for analysis. Hepatic fatty acids and triglycerides were measured by biochemical analysis, steatosis, inflammation and fibrosis scores were determined by a NAFLD scoring system (NAS) adapted from Kleiner et al (Hepatology 2005, 41(6), 1313-1321), and the percentage of fibrosis over total liver area was calculated based on the %Sirius Red labelling. The results are presented in the appended figures and discussed below.

Hepatic fatty acids

As can be seen from figure 1, lanifibranor treatment induced a dose-dependent decrease in hepatic fatty acids levels in the liver that reached statistical significance at 30 mg/kg. By contrast, tirzepatide treatment increased hepatic fatty acids levels in the liver. Treatment with a combination of lanifibranor and tirzepatide improved the initial response induced by the lanifibranor treatment at all doses administered, and reached statistical significance:

- for lanifibranor 10 mg/kg + tirzepatide 10 nmol/kg, compared to lanifibranor 10 mg/kg; and
- for lanifibranor 30 mg/kg + tirzepatide 3 nmol/kg, compared to lanifibranor 30 mg/kg.

Hepatic triglycerides

As can be seen from figure 2, lanifibranor treatment induced a dose-dependent decrease in hepatic triglycerides levels in the liver that reached statistical significance at 30 mg/kg. By contrast, tirzepatide treatment increased hepatic triglycerides levels in the liver. Treatment with a combination of lanifibranor and tirzepatide improved the initial response induced by lanifibranor, and reached statistical significance:

- for lanifibranor 10 mg/kg + tirzepatide 3 nmol/kg, compared to lanifibranor 10 mg/kg;
- for lanifibranor 10 mg/kg + tirzepatide 10 nmol/kg, compared to lanifibranor 10 mg/kg;
- for lanifibranor 30 mg/kg + tirzepatide 3 nmol/kg, compared to lanifibranor 30 mg/kg; and
- for lanifibranor 30mg/kg + tirzepatide 10 nmol/kg, compared to lanifibranor 30 mg/kg.

Steatosis score

As can be seen from figure 3, lanifibranor treatment induced a dose-dependent decrease in the liver steatosis score that reached statistical significance at 30 mg/kg. By contrast, tirzepatide has no effect on the liver steatosis score. Treatment with a combination of

lanifibranor and tirzepatide improved the initial response induced by lanifibranor, and reached statistical significance:

- for lanifibranor 10 mg/kg + tirzepatide 3 nmol/kg, compared to lanifibranor 10 mg/kg; and
- for lanifibranor 10 mg/kg + tirzepatide 10 nmol/kg, compared to lanifibranor 10 mg/kg.

5 *Inflammation score*

As can be seen from figure 4, lanifibranor treatment induced a dose-dependent decrease in the liver inflammation score that reached statistical significance at 10 mg/kg and 30 mg/kg. Tirzepatide also induced, but to a lesser extent, a statistically significant decrease in the liver inflammation score. Treatment with a combination of lanifibranor and tirzepatide further improved the initial response induced by lanifibranor, and reached statistical significance:

- for lanifibranor 10 mg/kg + tirzepatide 3 nmol/kg, compared to lanifibranor 10 mg/kg; and
- for lanifibranor 10 mg/kg + tirzepatide 10 nmol/kg, compared to lanifibranor 10 mg/kg.

Fibrosis score

As can be seen from figure 5, lanifibranor treatment induced a decrease in the liver fibrosis score at 30 mg/kg without reaching statistical significance. By contrast, tirzepatide treatment increased the liver fibrosis score. Treatment with a combination of lanifibranor and tirzepatide improved the initial response induced by lanifibranor. No statistical significance was reached when lanifibranor was used at 10 mg/kg. However, liver fibrosis was completely abrogated when lanifibranor was used at 30 mg/kg.

20 *Overall score*

As can be seen from figure 6, lanifibranor treatment induced a dose-dependent decrease for the overall score (liver steatosis + liver inflammation + fibrosis) that reached statistical significance at 30 mg/kg. Treatment with tirzepatide slightly decreased the overall score without reaching statistical significance. Treatment with a combination of lanifibranor and tirzepatide further improved the initial response induced by lanifibranor, and reached statistical significance:

- for lanifibranor 10 mg/kg + tirzepatide 3 nmol/kg, compared to lanifibranor 10 mg/kg; and
- for lanifibranor 10 mg/kg + tirzepatide 10 nmol/kg, compared to lanifibranor 10 mg/kg.

% of fibrosis over total liver area

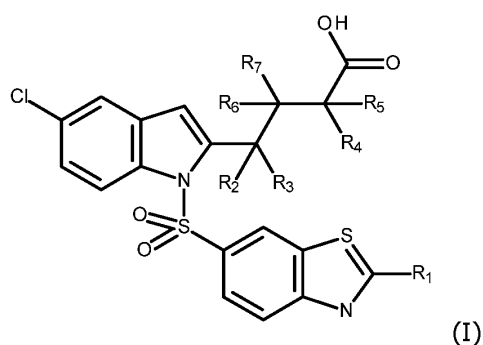
30 As can be seen from figure 7, lanifibranor treatment had no effect on the percentage of fibrosis over total liver area, whereas tirzepatide treatment increased such percentage. Treatment with a combination of lanifibranor 10 mg/kg and tirzepatide 3 nmol/kg, as well as with a combination of lanifibranor 30 mg/kg and tirzepatide at both doses, reduced the percentage of fibrosis over total liver area without reaching statistical significance. However

the data confirm those observed in figure 5 showing resolution of fibrosis when lanifibranor at 30 mg/kg is combined with tirzepatide at 3 nmol/kg or 10 nmol/kg.

The above results show that combining tirzepatide with lanifibranor provides an improvement of key fatty liver disease parameters. These results are unexpected in view of
5 the fact that tirzepatide *per se* has no effect on said parameters compared to vehicle.

Aspects of the present disclosure are further illustrated by reference to the following, non-limiting items.

1. A product comprising (i) lanifibranor or a deuterated form thereof and (ii) a
10 GLP-1/GIP dual receptor agonist.
2. The product of item 1, wherein lanifibranor or a deuterated form thereof is formulated in a first pharmaceutical composition and the GLP-1/GIP dual receptor agonist is formulated in a second, distinct, pharmaceutical composition.
3. The product of item 2, wherein the first pharmaceutical composition comprises from
15 about 0.5 mg to about 1,200 mg of lanifibranor or a deuterated form thereof.
4. The product of item 2 or item 3, wherein the second pharmaceutical composition comprises from about 0.01 mg to about 100 mg of GLP-1/GIP dual receptor agonist.
5. The product of any one of items 1 to 4, wherein lanifibranor or a deuterated form thereof and the GLP-1/GIP dual receptor agonist are intended to be administered to the
20 subject simultaneously, or wherein the lanifibranor or a deuterated form and the GLP-1/GIP dual receptor agonist are intended to be administered sequentially.
6. The product of item 1, wherein lanifibranor or a deuterated form thereof and the GLP-1/GIP dual receptor agonist are formulated in the same pharmaceutical composition.
7. The product of item 6, wherein the pharmaceutical composition comprises from about
25 0.5 mg to about 1,200 mg of lanifibranor or a deuterated form thereof, and from about 0.01 mg to about 100 mg of GLP-1/GIP dual receptor agonist and at least one pharmaceutically acceptable excipient.
8. The product of any one of items 1 to 7, wherein the deuterated form of lanifibranor is a compound of formula (I):



wherein at least one of the groups R₁ to R₇ is a deuterium (D) atom and the other groups R₁ to R₇ are hydrogen (H) atoms.

9. The product of item 8, wherein the deuterated form of lanifibranor is 4-(1-(2-
5 deuterio-1,3-benzothiazol-6-yl)sulfonyl)-5-chloro-1H-indol-2-yl)butanoic acid or 4-[1-(1,3-
benzothiazol-6-ylsulfonyl)-5-chloro-indol-2-yl]-2,2,3,3,4,4-hexadeuteriobutanoic acid.

10. The product of any one of items 1 to 9, wherein the GLP-1/GIP dual receptor agonist is selected from tirzepatide, VK2735, MAR709 and CT-388, preferably the GLP-1/GIP dual receptor agonist is tirzepatide.

10 11. The product of any one of items 1 to 10, wherein the product further comprises at
least one additional active pharmaceutical ingredient.

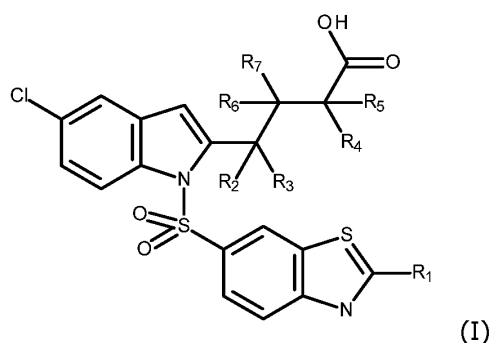
12. A combination of (i) lanifibranor or a deuterated form thereof and (ii) a GLP-1/GIP dual receptor agonist for use in the prevention and/or the treatment of a liver disease.

13. The combination for use of item 12, wherein the liver disease is selected from
15 cirrhosis, liver fibrosis, liver steatosis, fatty liver disease, acute decompensation, acute
decompensation of cirrhosis, acute-on-chronic liver failure, acute liver failure,
decompensated cirrhosis, compensated cirrhosis, non-alcoholic fatty liver disease, non-
alcoholic steatohepatitis, metabolic-associated fatty liver disease, metabolic-associated
steatohepatitis, non-cirrhotic non-alcoholic fatty liver disease, non-cirrhotic non-alcoholic
20 steatohepatitis, non-cirrhotic metabolic-associated fatty liver disease, non-cirrhotic
metabolic-associated steatohepatitis, autoimmune cholangitis, primary biliary cholangitis,
primary sclerosing cholangitis, autoimmune cholangiopathy, hepatocarcinoma, and liver
cirrhosis. and a combination of these diseases.

14. The combination for use of item 13, wherein the liver disease is selected from non-
25 alcoholic fatty liver disease, non-alcoholic steatohepatitis, metabolic-associated fatty liver
disease, metabolic-associated steatohepatitis, non-cirrhotic non-alcoholic fatty liver disease,
non-cirrhotic non-alcoholic steatohepatitis, non-cirrhotic metabolic-associated fatty liver
disease and non-cirrhotic metabolic-associated steatohepatitis.

15. The combination for use of items 13 or 14, wherein the liver disease is selected from non-alcoholic steatohepatitis with F0 stage of liver fibrosis, non-alcoholic steatohepatitis with F0/F1 stage of liver fibrosis, non-alcoholic steatohepatitis with F1 stage of liver fibrosis, non-alcoholic steatohepatitis with F1/F2 stage of liver fibrosis, non-alcoholic steatohepatitis with F2 stage of liver fibrosis, non-alcoholic steatohepatitis with F2/F3 stage of liver fibrosis, non-alcoholic steatohepatitis with F3 stage of liver fibrosis, non-alcoholic steatohepatitis with F3/F4 stage of liver fibrosis, non-alcoholic steatohepatitis with F4 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F0 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F0/F1 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F1 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F1/F2 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F2 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F2/F3 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F3 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F3/F4 stage of liver fibrosis, and non-cirrhotic non-alcoholic steatohepatitis with F4 stage of liver fibrosis
16. The combination for use of item 15, wherein the liver disease is non-alcoholic steatohepatitis with F2/F3 stage of liver fibrosis or non-cirrhotic non-alcoholic steatohepatitis with F2/F3 stage of liver fibrosis.
17. The combination for use of claim 13 or 14, wherein the liver disease is selected from metabolic-associated steatohepatitis with F0 stage of liver fibrosis, metabolic-associated steatohepatitis with F0/F1 stage of liver fibrosis, metabolic-associated steatohepatitis with F1 stage of liver fibrosis, metabolic-associated steatohepatitis with F1/F2 stage of liver fibrosis, metabolic-associated steatohepatitis with F2 stage of liver fibrosis, metabolic-associated steatohepatitis with F2/F3 stage of liver fibrosis, metabolic-associated steatohepatitis with F3 stage of liver fibrosis, metabolic-associated steatohepatitis with F3/F4 stage of liver fibrosis, metabolic-associated steatohepatitis with F4 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F0 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F0/F1 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F1 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F1/F2 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F2 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F2/F3 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F3 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F3/F4 stage of liver fibrosis, and non-cirrhotic metabolic-associated steatohepatitis with F4 stage of liver fibrosis.

18. The combination for use of item 17, wherein the liver disease is metabolic-associated steatohepatitis with F2/F3 stage of liver fibrosis or non-cirrhotic metabolic-associated steatohepatitis with F2/F3 stage of liver fibrosis.
19. The combination for use of any one of items 12 to 18, wherein the liver disease is associated with diabetes, in particular type 2 diabetes.
20. The combination for use of any one of items 12 to 19, wherein lanifibranor or a deuterated form thereof is formulated in a first pharmaceutical composition and the GLP-1/GIP dual receptor agonist is formulated in a second, distinct, pharmaceutical composition.
21. The combination for use of any one of items 12 to 20, wherein lanifibranor or a deuterated form thereof and the GLP-1/GIP dual receptor agonist are formulated in the same pharmaceutical composition.
22. The combination for use of any one of items 12 to 21, wherein lanifibranor or a deuterated form thereof and the GLP-1/GIP dual receptor agonist are intended to be administered simultaneously or sequentially.
23. The combination for use of any one of items 12 to 21, wherein lanifibranor or a deuterated form thereof and the GLP-1/GIP dual receptor agonist are intended to be administered over a period of time.
24. The combination for use of any one of items 12 to 23, wherein the GLP-1/GIP dual receptor agonist is selected from tirzepatide, VK2735, MAR709 and CT-388, preferably the GLP-1/GIP dual receptor agonist is tirzepatide.
25. The combination for use of any one of items 12 to 24, wherein the deuterated form of lanifibranor is a compound of formula (I):



- wherein at least one of the groups R_1 to R_7 is a deuterium (D) atom and the other groups R_1 to R_7 are hydrogen (H) atoms.

26. The combination of item 25, wherein the deuterated form of lanifibranor is 4-(1-(2-deuterio-1,3-benzothiazol-6-yl)sulfonyl)-5-chloro-1H-indol-2-yl)butanoic acid or 4-[1-(1,3-benzothiazol-6-ylsulfonyl)-5-chloro-indol-2-yl]-2,2,3,3,4,4-hexadeuteriobutanoic acid.
27. The combination for use of any one of items 12 to 26, wherein the combination
5 further comprises at least one additional active pharmaceutical ingredient.
28. A method of preventing and/or treating a liver disease, which comprises administering to a subject in need thereof (i) an effective amount of lanifibranor or a deuterated form thereof and (ii) an effective amount of a GLP-1/GIP dual receptor agonist.
29. The method of item 28, wherein the liver disease is selected from cirrhosis, liver
10 fibrosis, liver steatosis, fatty liver disease, acute decompensation, acute decompensation of cirrhosis, acute-on-chronic liver failure, acute liver failure, decompensated cirrhosis, compensated cirrhosis, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, metabolic-associated fatty liver disease, metabolic-associated steatohepatitis, non-cirrhotic non-alcoholic fatty liver disease, non-cirrhotic non-alcoholic steatohepatitis, non-cirrhotic
15 metabolic-associated fatty liver disease, non-cirrhotic metabolic-associated steatohepatitis, autoimmune cholangitis, primary biliary cholangitis, primary sclerosing cholangitis, autoimmune cholangiopathy, hepatocarcinoma, liver cirrhosis and a combination of these diseases..
30. The method of item 29, wherein the liver disease is selected from non-alcoholic fatty
20 liver disease, non-alcoholic steatohepatitis, metabolic-associated fatty liver disease, metabolic-associated steatohepatitis, non-cirrhotic non-alcoholic fatty liver disease, non-cirrhotic non-alcoholic steatohepatitis, non-cirrhotic metabolic-associated fatty liver disease and non-cirrhotic metabolic-associated steatohepatitis.
31. The method of items 29 or 30, wherein the liver disease is selected from non-
25 alcoholic steatohepatitis with F0 stage of liver fibrosis, non-alcoholic steatohepatitis with F0/F1 stage of liver fibrosis, non-alcoholic steatohepatitis with F1 stage of liver fibrosis, non-alcoholic steatohepatitis with F1/F2 stage of liver fibrosis, non-alcoholic steatohepatitis with F2 stage of liver fibrosis, non-alcoholic steatohepatitis with F2/F3 stage of liver fibrosis, non-
30 alcoholic steatohepatitis with F3 stage of liver fibrosis, non-alcoholic steatohepatitis with F3/F4 stage of liver fibrosis, non-alcoholic steatohepatitis with F4 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F0 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F0/F1 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F1 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F1/F2 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F2 stage of liver
35 fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F2/F3 stage of liver fibrosis, non-

cirrhotic non-alcoholic steatohepatitis with F3 stage of liver fibrosis, and non-cirrhotic non-alcoholic steatohepatitis with F3/F4 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F4 stage of liver fibrosis.

32. The method of item 31, wherein the liver disease is non-alcoholic steatohepatitis with
5 F2/F3 stage of liver fibrosis or non-cirrhotic non-alcoholic steatohepatitis with F2/F3 stage of liver fibrosis.

33. The method of items 29 or 30, wherein the liver is selected from metabolic-associated steatohepatitis with F0 stage of liver fibrosis, metabolic-associated steatohepatitis with F0/F1 stage of liver fibrosis, metabolic-associated steatohepatitis with F1 stage of liver fibrosis,
10 metabolic-associated steatohepatitis with F1/F2 stage of liver fibrosis, metabolic-associated steatohepatitis with F2 stage of liver fibrosis, metabolic-associated steatohepatitis with F2/F3 stage of liver fibrosis, metabolic-associated steatohepatitis with F3 stage of liver fibrosis, metabolic-associated steatohepatitis with F3/F4 stage of liver fibrosis, metabolic-associated steatohepatitis with F4 stage of liver fibrosis, non-cirrhotic metabolic-associated
15 steatohepatitis with F0 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F0/F1 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F1 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F1/F2 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F2 stage of liver fibrosis, non-cirrhotic metabolic-associated
20 steatohepatitis with F2/F3 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F3 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F3/F4 stage of liver fibrosis, and non-cirrhotic metabolic-associated steatohepatitis with F4 stage of liver fibrosis.

34. The method of item 33, wherein the liver disease is metabolic-associated
25 steatohepatitis with F2/F3 stage of liver fibrosis or non-cirrhotic metabolic-associated steatohepatitis with F2/F3 stage of liver fibrosis.

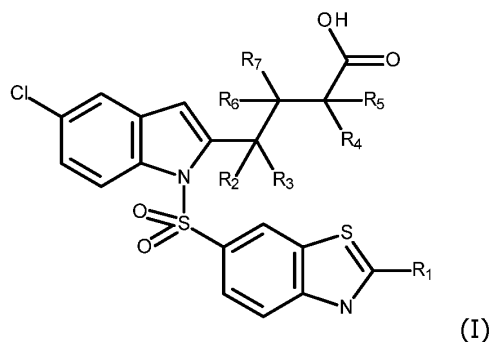
35. The method of any one of items 29 to 34, wherein the liver disease is associated with diabetes, in particular type 2 diabetes.

36. The method of any one of items 29 to 35, wherein lanifibranor or a deuterated form
30 thereof and the GLP-1/GIP dual receptor agonist are administered simultaneously or sequentially.

37. The method of any one of items 29 to 35, wherein lanifibranor or a deuterated form thereof and the GLP-1/GIP dual receptor agonist are administered over a period of time.

38. The method of any one of items 29 to 37, wherein the GLP-1/GIP dual receptor agonist is selected from tirzepatide, VK2735, MAR709 and CT-388, preferably the GLP-1/GIP dual receptor agonist is tirzepatide.

39. The method of any one of items 29 to 38, wherein the deuterated form of lanifibranor is a compound of formula (I):



wherein at least one of the groups R_1 to R_7 is a deuterium (D) atom and the other groups R_1 to R_7 are hydrogen (H) atoms.

40. The method of item 39, wherein the deuterated form of lanifibranor is 4-(1-(2-deuterio-1,3-benzothiazol-6-yl)sulfonyl)-5-chloro-1H-indol-2-yl)butanoic acid or 4-[1-(1,3-benzothiazol-6-ylsulfonyl)-5-chloro-indol-2-yl]-2,2,3,3,4,4-hexadeuteriobutanoic acid.

41. The method of any one of items 29 to 40, which further comprises administering to the subject an effective amount of (iii) at least one additional active pharmaceutical ingredient.

42. A method of preventing and/or treating a liver disease in a subject under treatment with lanifibranor or a deuterated form thereof, which comprises administering to the subject an effective amount of a GLP-1/GIP dual receptor agonist.

43. The method of item 42, wherein the liver disease is selected from cirrhosis, liver fibrosis, liver steatosis, fatty liver disease, acute decompensation, acute decompensation of cirrhosis, acute-on-chronic liver failure, acute liver failure, decompensated cirrhosis, compensated cirrhosis, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, metabolic-associated fatty liver disease, metabolic-associated steatohepatitis, non-cirrhotic non-alcoholic fatty liver disease, non-cirrhotic non-alcoholic steatohepatitis, non-cirrhotic metabolic-associated fatty liver disease, non-cirrhotic metabolic-associated steatohepatitis, autoimmune cholangitis, primary biliary cholangitis, primary sclerosing cholangitis, autoimmune cholangiopathy, hepatocarcinoma, liver cirrhosis and a combination of these diseases..

44. The method of item 43, wherein the liver disease is selected from non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, metabolic-associated fatty liver disease, metabolic-associated steatohepatitis, non-cirrhotic non-alcoholic fatty liver disease, non-cirrhotic non-alcoholic steatohepatitis, non-cirrhotic metabolic-associated fatty liver disease and non-cirrhotic metabolic-associated steatohepatitis.

45. The method of items 43 or 44, wherein the liver disease is selected from non-alcoholic steatohepatitis with F0 stage of liver fibrosis, non-alcoholic steatohepatitis with F0/F1 stage of liver fibrosis, non-alcoholic steatohepatitis with F1 stage of liver fibrosis, non-alcoholic steatohepatitis with F1/F2 stage of liver fibrosis, non-alcoholic steatohepatitis with F2 stage of liver fibrosis, non-alcoholic steatohepatitis with F2/F3 stage of liver fibrosis, non-alcoholic steatohepatitis with F3 stage of liver fibrosis, non-alcoholic steatohepatitis with F3/F4 stage of liver fibrosis, non-alcoholic steatohepatitis with F4 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F0 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F0/F1 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F1 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F1/F2 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F2 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F2/F3 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F3 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F3/F4 stage of liver fibrosis, and non-cirrhotic non-alcoholic steatohepatitis with F4 stage of liver fibrosis.

46. The method of item 45, wherein the liver disease is non-alcoholic steatohepatitis with F2/F3 stage of liver fibrosis or non-cirrhotic non-alcoholic steatohepatitis with F2/F3 stage of liver fibrosis.

47. The method of items 43 or 44, wherein the liver disease is selected from metabolic-associated steatohepatitis with F0 stage of liver fibrosis, metabolic-associated steatohepatitis with F0/F1 stage of liver fibrosis, metabolic-associated steatohepatitis with F1 stage of liver fibrosis, metabolic-associated steatohepatitis with F1/F2 stage of liver fibrosis, metabolic-associated steatohepatitis with F2 stage of liver fibrosis, metabolic-associated steatohepatitis with F2/F3 stage of liver fibrosis, metabolic-associated steatohepatitis with F3 stage of liver fibrosis, metabolic-associated steatohepatitis with F3/F4 stage of liver fibrosis, metabolic-associated steatohepatitis with F4 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F0 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F0/F1 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F1 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F1/F2 stage of liver fibrosis, non-cirrhotic metabolic-associated

steatohepatitis with F2 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F2/F3 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F3 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F3/F4 stage of liver fibrosis, and non-cirrhotic metabolic-associated steatohepatitis with F4 stage of liver fibrosis.

48. The method of item 47, wherein the liver disease is metabolic-associated steatohepatitis with F2/F3 stage of liver fibrosis or non-cirrhotic metabolic-associated steatohepatitis with F2/F3 stage of liver fibrosis.

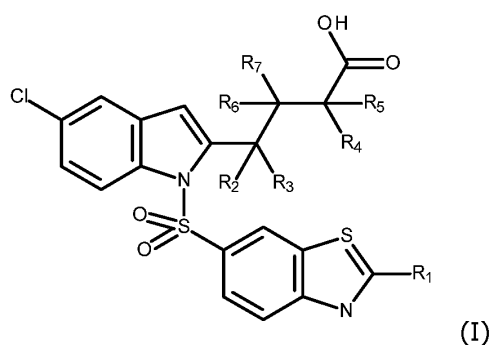
49. The method of any one of items 42 to 48, wherein the liver disease is associated with diabetes, in particular type 2 diabetes.

50. The method of any one of items 42 to 49, wherein lanifibranor or a deuterated form thereof and the GLP-1/GIP dual receptor agonist are administered simultaneously or sequentially.

51. The method of any one of items 42 to 50, wherein lanifibranor or a deuterated form thereof and the GLP-1/GIP dual receptor agonist are administered over a period of time.

52. The method of any one of items 42 to 51, wherein the GLP-1/GIP dual receptor agonist is selected from tirzepatide, VK2735, MAR709 and CT-388, preferably the GLP-1/GIP dual receptor agonist is tirzepatide.

53. The method of any one of items 42 to 52, wherein the deuterated form of lanifibranor is a compound of formula (I):



wherein at least one of the groups R_1 to R_7 is a deuterium (D) atom and the other groups R_1 to R_7 are hydrogen (H) atoms.

54. The method of item 53, wherein the deuterated form of lanifibranor is 4-(1-(2-deuterio-1,3-benzothiazol-6-yl)sulfonyl)-5-chloro-1H-indol-2-yl)butanoic acid or 4-[1-(1,3-benzothiazol-6-ylsulfonyl)-5-chloro-indol-2-yl]-2,2,3,3,4,4-hexadeuteriobutanoic acid.

55. The method of any one of items 42 to 54, wherein the method further comprises administering to the subject an effective amount at least one additional active pharmaceutical ingredient.

56. A method of preventing and/or treating a liver disease in a subject under
5 GLP-1/GIP dual receptor agonist treatment, which comprises administering to the subject an effective amount of lanifibranor or a deuterated form thereof.

57. The method of item 56, wherein the liver disease is selected from cirrhosis, liver fibrosis, liver steatosis, fatty liver disease, acute decompensation, acute decompensation of cirrhosis, acute-on-chronic liver failure, acute liver failure, decompensated cirrhosis,
10 compensated cirrhosis, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, metabolic-associated fatty liver disease, metabolic-associated steatohepatitis, non-cirrhotic non-alcoholic fatty liver disease, non-cirrhotic non-alcoholic steatohepatitis, non-cirrhotic metabolic-associated fatty liver disease, non-cirrhotic metabolic-associated steatohepatitis, autoimmune cholangitis, primary biliary cholangitis, primary sclerosing cholangitis,
15 autoimmune cholangiopathy, hepatocarcinoma, liver cirrhosis and a combination of these diseases..

58. The method of item 57, wherein the liver disease is selected from non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, metabolic-associated fatty liver disease, metabolic-associated steatohepatitis, non-cirrhotic non-alcoholic fatty liver disease, non-
20 cirrhotic non-alcoholic steatohepatitis, non-cirrhotic metabolic-associated fatty liver disease and non-cirrhotic metabolic-associated steatohepatitis.

59. The method of items 57 or 58, wherein the liver is selected from non-alcoholic steatohepatitis with F0 stage of liver fibrosis, non-alcoholic steatohepatitis with F0/F1 stage of liver fibrosis, non-alcoholic steatohepatitis with F1 stage of liver fibrosis, non-alcoholic steatohepatitis with F1/F2 stage of liver fibrosis, non-alcoholic steatohepatitis with F2 stage of liver fibrosis, non-alcoholic steatohepatitis with F2/F3 stage of liver fibrosis, non-alcoholic steatohepatitis with F3 stage of liver fibrosis, non-alcoholic steatohepatitis with F3/F4 stage of liver fibrosis, non-alcoholic steatohepatitis with F4 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F0 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F0/F1 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F1 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F1/F2 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F2 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F2/F3 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F3 stage of liver fibrosis, non-cirrhotic non-alcoholic
30 steatohepatitis with F3 stage of liver fibrosis, non-cirrhotic non-alcoholic

steatohepatitis with F3/F4 stage of liver fibrosis, and non-cirrhotic non-alcoholic steatohepatitis with F4 stage of liver fibrosis.

60. The method of item 59, wherein the liver disease is non-alcoholic steatohepatitis with F2/F3 stage of liver fibrosis or non-cirrhotic non-alcoholic steatohepatitis with F2/F3 stage of liver fibrosis.

61. The method of items 57 or 58, wherein the liver disease is selected from metabolic-associated steatohepatitis with F0 stage of liver fibrosis, metabolic-associated steatohepatitis with F0/F1 stage of liver fibrosis, metabolic-associated steatohepatitis with F1 stage of liver fibrosis, metabolic-associated steatohepatitis with F1/F2 stage of liver fibrosis, metabolic-associated steatohepatitis with F2 stage of liver fibrosis, metabolic-associated steatohepatitis with F2/F3 stage of liver fibrosis, metabolic-associated steatohepatitis with F3 stage of liver fibrosis, metabolic-associated steatohepatitis with F3/F4 stage of liver fibrosis, metabolic-associated steatohepatitis with F4 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F0 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F0/F1 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F1 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F1/F2 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F2 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F2/F3 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F3 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F3/F4 stage of liver fibrosis, and non-cirrhotic metabolic-associated steatohepatitis with F4 stage of liver fibrosis.

62. The method of item 61, wherein the liver disease is metabolic-associated steatohepatitis with F2/F3 stage of liver fibrosis or non-cirrhotic metabolic-associated steatohepatitis with F2/F3 stage of liver fibrosis.

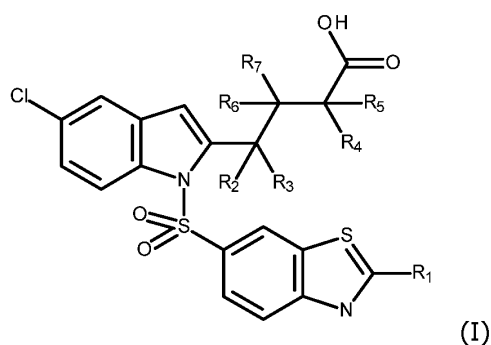
63. The method of any one of items 56 to 62, wherein the liver disease is associated with diabetes, in particular type 2 diabetes.

64. The method of any one of items 56 to 63, wherein the GLP-1/GIP dual receptor agonist and lanifibranor or a deuterated form thereof are administered simultaneously or sequentially.

65. The method of any one of items 56 to 63, wherein the GLP-1/GIP dual receptor agonist and lanifibranor or a deuterated form thereof are administered over a period of time.

66. The method of any one of items 56 to 65, wherein the GLP-1/GIP dual receptor agonist is selected from tirzepatide, VK2735, MAR709 and CT-388, preferably the GLP-1/GIP dual receptor agonist is tirzepatide.

67. The method of any one of items 56 to 66, wherein the deuterated form of lanifibranor is a compound of formula (I):



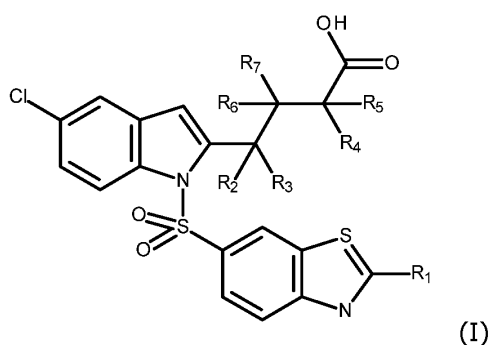
wherein at least one of the groups R_1 to R_7 is a deuterium (D) atom and the other groups R_1 to R_7 are hydrogen (H) atoms.

68. The method of item 67, wherein the deuterated form of lanifibranor is 4-(1-(2-deuterio-1,3-benzothiazol-6-yl)sulfonyl)-5-chloro-1H-indol-2-yl)butanoic acid or 4-[1-(1,3-benzothiazol-6-ylsulfonyl)-5-chloro-indol-2-yl]-2,2,3,3,4,4-hexadeuteriobutanoic acid.

69. The method of any one of items 56 to 68, wherein the method further comprises administering to the subject an effective amount at least one additional active pharmaceutical ingredient.

CLAIMS

1. A product comprising (i) lanifibranor or a deuterated form thereof and (ii) a GLP-1/GIP dual receptor agonist.
5
2. The product of claim 1, wherein lanifibranor or a deuterated form thereof is formulated in a first pharmaceutical composition and the GLP-1/GIP dual receptor agonist is formulated in a second, distinct, pharmaceutical composition.
- 10 3. The product of claim 2, wherein the first pharmaceutical composition comprises from about 0.5 mg to about 1,200 mg of lanifibranor or a deuterated form thereof.
4. The product of claim 2 or claim 3, wherein the second pharmaceutical composition comprises from about 0.01 mg to about 100.0 mg of GLP-1/GIP dual receptor agonist.
15
5. The product of any one of claims 1 to 4, wherein lanifibranor or a deuterated form thereof and the GLP-1/GIP dual receptor agonist are intended to be administered to the subject simultaneously, or wherein the lanifibranor or a deuterated form and the GLP-1/GIP dual receptor agonist are intended to be administered sequentially, or wherein
20 the lanifibranor or a deuterated form and the GLP-1/GIP dual receptor agonist are intended to be administered over a period of time.
6. The product of claim 1, wherein lanifibranor or a deuterated form thereof and the GLP-1/GIP dual receptor agonist are formulated in the same pharmaceutical composition.
25
7. The product of claim 6, wherein the pharmaceutical composition comprises from about 0.5 mg to about 1,200 mg of lanifibranor or a deuterated form thereof, and from about 0.01 mg to about 100.0 mg of GLP-1/GIP dual receptor agonist.
- 30 8. The product of any one of claims 1 to 7, wherein the deuterated form of lanifibranor is a compound of formula (I):



wherein at least one of the groups R_1 to R_7 is a deuterium (D) atom and the other groups R_1 to R_7 are hydrogen (H) atoms.

- 5 9. The product of any one of claims 1 to 8, wherein the GLP-1/GIP dual receptor agonist is selected from tirzepatide, VK2735, MAR709 and CT-388, preferably the GLP-1/GIP dual receptor agonist is tirzepatide.
- 10 10. The product of any one of claims 1 to 9, wherein the product further comprises at least one additional active pharmaceutical ingredient.
11. A combination of (i) lanifibranor or a deuterated form thereof and (ii) a GLP-1/GIP dual receptor agonist for use in the prevention and/or the treatment of a liver disease.
- 15 12. The combination for use of claim 11, wherein the liver disease is selected from cirrhosis, liver fibrosis, liver steatosis, fatty liver disease, acute decompensation, acute decompensation of cirrhosis, acute-on-chronic liver failure, acute liver failure, decompensated cirrhosis, compensated cirrhosis, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, metabolic-associated fatty liver disease, metabolic-associated steatohepatitis, non-cirrhotic non-alcoholic fatty liver disease, non-cirrhotic non-alcoholic steatohepatitis, non-cirrhotic metabolic-associated fatty liver disease, non-cirrhotic metabolic-associated steatohepatitis, autoimmune cholangitis, primary biliary cholangitis, primary sclerosing cholangitis, autoimmune cholangiopathy, hepatocarcinoma, liver cirrhosis and a combination of these diseases.
- 20 13. The combination for use of claim 12, wherein the liver disease is selected from non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, metabolic-associated fatty liver disease, metabolic-associated steatohepatitis, non-cirrhotic non-alcoholic fatty liver disease,
- 25

non-cirrhotic non-alcoholic steatohepatitis, non-cirrhotic metabolic-associated fatty liver disease and non-cirrhotic metabolic-associated steatohepatitis.

14. The combination for use of claim 12 or 13, wherein the liver disease is selected from non-alcoholic steatohepatitis with F0 stage of liver fibrosis, non-alcoholic steatohepatitis with F0/F1 stage of liver fibrosis, non-alcoholic steatohepatitis with F1 stage of liver fibrosis, non-alcoholic steatohepatitis with F1/F2 stage of liver fibrosis, non-alcoholic steatohepatitis with F2 stage of liver fibrosis, non-alcoholic steatohepatitis with F2/F3 stage of liver fibrosis, non-alcoholic steatohepatitis with F3 stage of liver fibrosis, non-alcoholic steatohepatitis with F3/F4 stage of liver fibrosis, non-alcoholic steatohepatitis with F4 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F0 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F0/F1 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F1 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F1/F2 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F2 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F2/F3 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F3 stage of liver fibrosis, non-cirrhotic non-alcoholic steatohepatitis with F3/F4 stage of liver fibrosis, and non-cirrhotic non-alcoholic steatohepatitis with F4 stage of liver fibrosis.
15. The combination for use of claim 12 or 13, wherein the liver disease is selected from metabolic-associated steatohepatitis with F0 stage of liver fibrosis, metabolic-associated steatohepatitis with F0/F1 stage of liver fibrosis, metabolic-associated steatohepatitis with F1 stage of liver fibrosis, metabolic-associated steatohepatitis with F1/F2 stage of liver fibrosis, metabolic-associated steatohepatitis with F2 stage of liver fibrosis, metabolic-associated steatohepatitis with F2/F3 stage of liver fibrosis, metabolic-associated steatohepatitis with F3 stage of liver fibrosis, metabolic-associated steatohepatitis with F3/F4 stage of liver fibrosis, metabolic-associated steatohepatitis with F4 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F0 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F0/F1 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F1 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F1/F2 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F2 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F2/F3 stage of liver fibrosis, non-cirrhotic metabolic-associated steatohepatitis with F3 stage of liver fibrosis, non-cirrhotic metabolic-associated

steatohepatitis with F3/F4 stage of liver fibrosis, and non-cirrhotic metabolic-associated steatohepatitis with F4 stage of liver fibrosis.

16. The combination for use of any one of claims 11 to 15, wherein the liver disease is associated with diabetes, in particular type 2 diabetes.

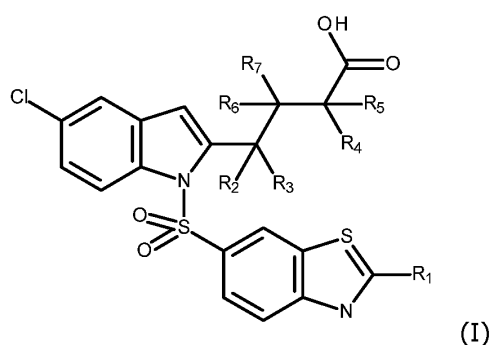
17. The combination for use of any one of claims 11 to 16, wherein lanifibranor or a deuterated form thereof is formulated in a first pharmaceutical composition and the GLP-1/GIP dual receptor agonist is formulated in a second, distinct, pharmaceutical composition.

18. The combination for use of any one of claims 11 to 17, wherein lanifibranor or a deuterated form thereof and the GLP-1/GIP dual receptor agonist are formulated in the same pharmaceutical composition.

19. The combination for use of any one of claims 11 to 18, wherein lanifibranor or a deuterated form thereof and the GLP-1/GIP dual receptor agonist are intended to be administered simultaneously or sequentially.

20. The combination for use of any one of claims 11 to 18, wherein lanifibranor or a deuterated form thereof and the GLP-1/GIP dual receptor agonist are intended to be administered over a period of time.

21. The combination for use of any one of claims 11 to 20, wherein the deuterated form of lanifibranor is a compound of formula (I):



wherein at least one of the groups R_1 to R_7 is a deuterium (D) atom and the other groups R_1 to R_7 are hydrogen (H) atoms.

22. The combination for use of any one of claims 11 to 21, wherein the GLP-1/GIP agonist is selected from tirzepatide, VK2735, MAR709 and CT-388, preferably the GLP-1/GIP dual receptor agonist is tirzepatide.

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23. The combination for use of any one of claims 11 to 22, wherein the combination further comprises at least one additional active pharmaceutical ingredient.