PREVENTION OF BLOOD DISORDERS IN PATIENT TREATED WITH A PPAR AGONIST.

FIELD OF THE INVENTION

The present disclosure relates to sodium glucose transporter 2 (SGLT2) inhibitors for use in the prevention or delay of clinical complications of blood disorders, and preferably anaemia or clinical complications of anaemia, in patients having been treated, treated or planned to be treated with a PPAR agonist.

BACKGROUND OF THE INVENTION

Peroxisome proliferator-activated receptors (PPARs) are a well-known pharmacological target for the treatment of multiple diseases, including diabetes mellitus, dyslipidemia, cardiovascular diseases and even primary biliary cholangitis, gout, cancer, Alzheimer's disease and ulcerative colitis. The three PPAR isoforms (α, β/δ and γ) have emerged as integrators of glucose and lipid metabolic signaling networks. In the liver, PPARs play indispensable roles in fatty-acid and glucose metabolism, and they supply energy to peripheral tissues. Despite the multiple biological activities of PPARs, several studies and clinical cases indicated that PPARs mediate various side effects of drugs, especially PPAR agonists.

There is therefore a need for methods, medicaments and pharmaceutical compositions which allow treating the liver diseases effectively, while reducing or avoiding the side effects associated with PPAR agonist treatments, in particular, blood disorders side effects and more preferably anaemia or clinical complications of anaemia.

SUMMARY OF THE INVENTION

In one aspect, the present disclosure relates to sodium glucose transporter 2 (SGLT2) inhibitor for use in the prevention or delay of anaemia or clinical complications of anaemia in patient treated, planned to be treated or having been treated with a PPAR agonist.

In one aspect the present disclosure relates to a method for preventing or delaying anaemia or clinical complications of anaemia in a patient having been treated, treated or planned to be treated with a PPAR agonist, the method comprising administering to the patient a suitable dosage of a SGLT2 inhibitor.

In one aspect, the present disclosure relates to a method for preventing a reduction in the amount of hemoglobin in a patient having been treated, treated or planned to be treated with a PPAR agonist, the method comprising administering to the patient a suitable dosage of SGLT2 inhibitor.

In one aspect, the present disclosure relates to a method for reducing or preventing the discontinuation of a treatment with a PPAR agonist in a patient treated with such

PPAR agonist, the method comprising administering to the patient a suitable dosage of a SGLT2 inhibitor.

In some embodiments of the use or methods above, the patient is treated or is planned to be treated with a PPAR agonist and the first dose of SGLT2 inhibitor is (a) administered at least one day after the start of the treatment with the PPAR agonist; or (b) administered at the same time as the first dose of the treatment with the PPAR agonist; or (c) administered at least one day before the start of the treatment with the PPAR agonist.

In some embodiments of the use or methods above, the PPAR agonist is lanifibranor, a deuterated form of lanifibranor or a pharmaceutically acceptable salt thereof.

In some embodiments of the use or methods above, the SGLT2 inhibitor is empagliflozin or a pharmaceutically acceptable salt thereof.

Definitions

As used herein, the articles "a" and "an" refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

As used herein, the use of the term "including" as well as other forms, such as "include," "includes," and "included," is not limiting.

As used herein, the term "comprising" can include the embodiments "consisting of' and "consisting essentially of." The terms "comprise(s)," "include(s)," "having," "has," "can," "contain(s)," and variants thereof, as used herein, are intended to be open-ended transitional phrases, terms, or words that require the presence of the named ingredients/steps and permit the presence of other ingredients/steps. However, such description should be construed as also describing compositions or processes as "consisting of' and "consisting essentially of" the enumerated compounds, which allows the presence of only the named compounds, along with any pharmaceutically acceptable carriers, and excludes other compounds.

As used herein, the term "about xx" refers to a measurable value such as a parameter, an amount, a temporal duration, and the like, is meant to encompass variations of +/-10% or less, preferably +/-5% or less, more preferably +/-1% or less, even more preferably +/-0.5% or less, more preferably +/-0.05% or less, and still more preferably +/-0.04% or less, +/-0.03% or less, +/-0.02% or less, +/-0.01% or less of and from the specified value, insofar such variations are appropriate to perform in the disclosed invention. However, it is to be understood that the value to which "about" refers is itself also specifically disclosed. In other words, the term "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 "treatment" or "treating" refers to any process, action, application, therapy, or the like, wherein the patient is under aid, in particular, medical, or veterinarian 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, the term "prevention" or "prophylaxis" or "preventative treatment" or "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 "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 may be a child (human patient 18 years of age or younger) or an adult (human patient over 18 years of age). 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 "patient" and "subject" are used interchangeably.

When used with respect to methods of treatment and the use of the compounds and pharmaceutical compositions thereof described herein, a patient "in need thereof' may be a patient who has been diagnosed with or previously treated for the condition to be treated. Typically, when a step of administering a compound provided herein, the method further contemplates a step of identifying a patient or subject in need of the particular treatment to be administered or having the particular condition to be treated.

As used herein, the term "pharmaceutically acceptable" refers to a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound, and is relatively non-toxic, i.e., the material can be administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

The terms "level" and "amount" are used herein interchangeably to mean the concentration of biomarker present in a sample.

As used herein, the term "reference amount" or "reference level" is the amount of a biomarker in a sample obtained from a patient, said sample being obtained from the

patient prior the first administration of lanifibranor treatment, in particular this sample is obtained at the baseline visit.

As used herein, the term "pharmaceutically acceptable salts" refers to salts that retain the biological effectiveness and properties of the compounds with which they are associated and, which are not biologically or otherwise undesirable. In many cases, the compounds herein are capable of forming acid and/or base salts by virtue of the presence of phenol and/or phosphonate groups or groups similar thereto. One of ordinary skill in the art will be aware that the protonation state of any or all of these compounds may vary with pH and ionic character of the surrounding solution, and thus the present disclosure contemplates multiple charge states of each compound. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like; particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and Journal of Pharmaceutical Science, 66, 2 (1977), each of which is incorporated herein by reference in its entirety.

As used herein, "solvate" refers to the compound formed by the interaction of a solvent and an active pharmaceutical ingredient (API), a metabolite, or salt thereof. Suitable solvates are pharmaceutically acceptable solvates including hydrates.

As used herein, "suitable dosage" means a suitable amount of SGLT2 inhibitor, given to the patient for preventing blood disorders at one specific time, or for reducing or preventing the discontinuation of a treatment with a PPAR agonist. Within the context of the present invention, "dosage", "dose" and "amount" are interchangeable.

As used herein, the term "tablet" comprises tablets without a coating and tablets with one or more coatings. Furthermore the "term" tablet comprises tablets having one, two, three or even more layers and press-coated tablets, wherein each of the beforementioned types of tablets may be without or with one or more coatings. The term "tablet" also comprises mini, melt, chewable, effervescent and orally disintegrating tablets.

DETAILLED DESCRIPTION

The present disclosure provides a new use of sodium glucose transporter 2 (SGLT2) inhibitor. In particular, the present disclosure relates to a sodium glucose transporter 2 (SGLT2) inhibitor for use in the prevention or delay of clinical complications of blood disorders in patient having been treated, treated or planned to be treated with a PPAR agonist. In particular, the present disclosure relates to a sodium glucose transporter 2 (SGLT2) inhibitor for use in the prevention or delay of anaemia or clinical complications of anaemia in patient having been treated, treated or planned to be treated with a PPAR agonist.

The inventors have surprisingly demonstrated that SGLT2 inhibitor inhibits and/or compensate the decrease of hemoglobin and ferritin observed in patient having been treated, treated or planned to be treated with a PPAR agonist. Moreover, the inventors have surprisingly demonstrated that SGLT2 inhibitor inhibits and/or compensate the weight gain observed in patient having been treated, treated or planned to be treated with a PPAR agonist.

As used herein, the term "SGLT2 inhibitor" or "sodium glucose transporter 2 inhibitor" in the scope of the present disclosure relates to a compound, in particular to a glucopyranosyl-derivative, i.e. a compound having a glucopyranosyl-moiety, which shows an inhibitory effect on the sodium-glucose transporter 2 (SGLT2), in particular the human SGLT2. The inhibitory effect on hSGLT2 measured as IC_{50} is preferably below 1000 nM, even more preferably below 100 nM, most preferably below 50 nM. IC_{50} values of SGLT2 inhibitors are usually above 0.01 nM, or even equal to or above 0.1 nM. The inhibitory effect on hSGLT2 can be determined by methods known in the literature, in particular as described in the application WO 2005/092877 or WO 2007/093610. The term "SGLT2 inhibitor" also comprises any pharmaceutically acceptable salts thereof, hydrates and solvates thereof, including the respective crystalline forms. Examples of SGLT2 inhibitors are canaglifozin, dapagliflozin, remoglifozin, sergliflozin, empagliflozin, ipragliflozin, tofogliflozin, luseogliflozin, sotagliflozin, ertuglifozin, bexagliflozin, henagliflozin, janagliflozin and tianagliflozin, including prodrugs, pharmaceutically acceptable salts, hydrate and solvates thereof. Prodrugs thereof are for example remogliflozin etabonate and sergliflozin etabonate.

In some embodiments, the SGLT2 inhibitor is selected from the group comprising canaglifozin, dapagliflozin, remoglifozin, sergliflozin, empagliflozin, ipragliflozin, tofogliflozin, luseogliflozin, sotagliflozin, ertuglifozin, bexagliflozin, henagliflozin, janagliflozin, tianagliflozin, a pharmaceutically acceptable salt thereof and a mixture of them. In some embodiments, the SGLT2 inhibitor is empagliflozin, including hydrate and solvates thereof. The term "empagliflozin" refers to the SGLT2 inhibitor 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((S)-tetrahydrofuran-3-yloxy)-benzyl]-benzene of the formula as described for example in WO2005/092877. Methods of synthesis are described in the literature, for example WO2006/120208 and WO2011/039108. According to this invention, it is to be understood that the definition of empagliflozin also comprises its hydrates, solvates and polymorphic forms thereof, and prodrugs thereof. An advantageous crystalline form of empagliflozin is described in WO2006/117359 and WO2011/039107 which hereby are incorporated herein in their entirety. Preferred pharmaceutical compositions, such as solid formulations for oral administration, for example tablets, are described in WO2010/092126, which hereby is incorporated herein in its entirety.

As used herein, the term “blood disorders” refers to any disorder related to blood, including, but not limited to anaemia. In some embodiments, the blood disorders are a reduction in the amount of at least one biomarker compared to the reference amount of said at least one biomarker, wherein the at least one biomarker is selected from: hemoglobin, ferritin, haptoglobin, unsaturated iron binding capacity, iron, lactate dehydrogenase, hematocrit, transferrin, vitamin B12, vitamin B9 and a combination thereof. In a preferred embodiment, the blood disorders are anaemia or clinical complications of anaemia. As used herein, the term “anaemia” or clinical complication of anaemia” refers to a reduction in the amount of at least one biomarker compared to the reference amount of said at least one biomarker, wherein the at least one biomarker is selected from: hemoglobin, ferritin, haptoglobin, unsaturated iron binding capacity, iron, lactate dehydrogenase, hematocrit, transferrin, vitamin B12, vitamin B9 and a combination thereof.

In some embodiments, the reduction in the amount of at least one biomarker is greater than or equal to 1% compared to the reference amount of at least one biomarker of said patient. In some embodiments, the reduction in the amount of at least one biomarker is greater than or equal to 2%, for example greater than or equal to 3%, for example greater than or equal to 4%, for example greater than or equal to 5%, for example greater than or equal to 6%, for example greater than or equal to 7%, for example greater than or equal to 8%, for example greater than or equal to 9%, for example greater than or equal to 10%, for example greater than or equal to

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In some embodiments, the blood disorders are a reduction in the amount of hemoglobin of at least 1% to at least 70% compared to the reference amount of hemoglobin. In some embodiments, the blood disorders are a reduction in the amount of ferritin of at least 1% to at least 70% compared to the reference amount of ferritin. In some embodiments, the blood disorders are a reduction in the amount of iron of at least 1% to at least 70% compared to the reference amount of iron. In some

embodiments, the blood disorders are a reduction in the amount of haptoglobin of at least 1% to at least 70% compared to the reference amount of haptoglobin. In some embodiments, the blood disorders are a reduction in the amount of transferrin of at least 1% to at least 70% compared to the reference amount of transferrin. In some embodiments, the blood disorders are a reduction in the amount of vitamin B12 of at least 1% to at least 70% compared to the reference amount of vitamin B12. In some embodiments, the blood disorders are a reduction in the amount of vitamin B9 of at least 1% to at least 70% compared to the reference amount of vitamin B9. In some embodiments, the blood disorders are a reduction in the amount of hematocrit of at least 1% to at least 70% compared to the reference amount of hematocrit. In a preferred embodiment, the blood disorders are anaemia or clinical complications of anaemia. In some embodiments, anaemia or clinical complications of anaemia are due to a reduction in the amount of hemoglobin of at least 1% to at least 70% compared to the reference amount of hemoglobin. In some embodiments, anaemia or clinical complications of anaemia are due to a reduction in the amount of ferritin of at least 1% to at least 70% compared to the reference amount of ferritin. In some embodiments, anaemia or clinical complications of anaemia are due to a reduction in the amount of iron of at least 1% to at least 70% compared to the reference amount of iron. In some embodiments, anaemia or clinical complications of anaemia are due to a reduction in the amount of haptoglobin of at least 1% to at least 70% compared to the reference amount of haptoglobin. In some embodiments, anaemia or clinical complications of anaemia are due to a reduction in the amount of transferrin of at least 1% to at least 70% compared to the reference amount of transferrin. In some embodiments, anaemia or clinical complications of anaemia are due to a reduction in the amount of vitamin B12 of at least 1% to at least 70% compared to the reference amount of vitamin B12. In some embodiments, anaemia or clinical complications of anaemia are due to a reduction in the amount of vitamin B9 of at least 1% to at least 70% compared to the reference amount of vitamin B9. In some embodiments, anaemia or clinical complications of anaemia are due to a reduction in the amount of hematocrit of at least 1% to at least 70% compared to the reference amount of hematocrit.

In some embodiments, the blood disorders are a reduction in the amount of a combination of biomarkers as defined above, wherein the reduction in the amount of the combination of biomarkers is of at least 1% to at least 70% compared to the reference amount of said combination. In some embodiments, anaemia or clinical complications of anaemia are due to a reduction in the amount of a combination of biomarkers as defined above, wherein the reduction in the amount of the combination

of biomarkers is of at least 1% to at least 70% compared to the reference amount of said combination. In some embodiments, a combination of biomarkers comprises at least 2 biomarkers selected from: hemoglobin, ferritin, haptoglobin, hematocrit, transferrin, vitamin B12 and vitamin B9. In some embodiments, a combination of biomarkers comprises at least 3, at least 4, at least 5, at least 6 or at least 7 biomarkers selected from: hemoglobin, ferritin, haptoglobin, hematocrit, transferrin, vitamin B12 and vitamin B9. In some embodiments, a combination of biomarkers comprises at least hemoglobin and one of the following biomarkers selected from: ferritin, haptoglobin, hematocrit, transferrin, vitamin B12 and vitamin B9. In some embodiments, a combination of biomarkers comprises at least hemoglobin and ferritin and optionally one of the following biomarkers selected from: haptoglobin, hematocrit, transferrin, vitamin B12 and vitamin B9. In some embodiments, a combination of biomarkers comprises at least hemoglobin, ferritin and haptoglobin, and optionally one of the following biomarkers selected from: hematocrit, transferrin, vitamin B12 and vitamin B9. In some embodiments, a combination of biomarkers comprises at least hemoglobin, ferritin, haptoglobin and hematocrit, and optionally one of the following biomarkers selected from: transferrin, vitamin B12 and vitamin B9. In some embodiments, a combination of biomarkers comprises at least hemoglobin, ferritin, haptoglobin, hematocrit and transferrin, and optionally one of the following biomarkers selected from: vitamin B12 and vitamin B9. In some embodiments, a combination of biomarkers comprises hemoglobin, ferritin, haptoglobin, hematocrit, transferrin and vitamin B9. In some embodiments, a combination of biomarkers comprises hemoglobin and ferritin. In some embodiments, a combination of biomarkers solely comprises hemoglobin and ferritin. In some embodiments, a combination of biomarkers comprises hemoglobin, ferritin, haptoglobin, hematocrit, transferrin, and vitamin B12.

In some embodiments, the reduction in the amount of hemoglobin is equal to or greater than 1%, for example equal to or greater than 2%, for example equal to or greater than 3%, for example equal to or greater than 4%, for example equal to or greater than 5%, for example equal to or greater than 6%, for example equal to or greater than 7%, for example equal to or greater than 8%, for example equal to or greater than 9%, for example equal to or greater than 10%, for example equal to or greater than 11%, for example equal to or greater than 12%, for example equal to or greater than 13%, for example equal to or greater than 14%, for example equal to or greater than 15%, for example equal to or greater than 16%, for example equal to or greater than 17%, for example equal to or greater than 18%, for example equal to or greater than 19%, for example equal to or greater than 20%, for example equal to or

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In some embodiments, the reduction in the amount of ferritin is equal to or greater than 1%, for example equal to or greater than 2%, for example equal to or greater than 3%, for example equal to or greater than 4%, for example equal to or greater than 5%, for example equal to or greater than 6%, for example equal to or greater than 7%, for example equal to or greater than 8%, for example equal to or greater than 9%, for example equal to or greater than 10%, for example equal to or greater than 11%, for example equal to or greater than 12%, for example equal to or greater than 13%, for example equal to or greater than 14%, for example equal to or greater than 15%, for example equal to or greater than 16%, for example equal to or greater

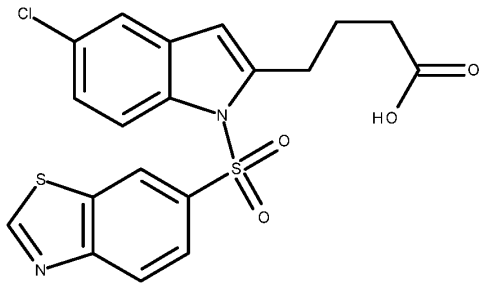
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In some embodiments, the blood disorders can consist in hemoglobin abnormalities.

As used herein, the term "PPAR agonist" refers to PPARα agonist, PPARγ agonist, PPARδ agonist, PPARα/δ dual agonist, PPARα/γ dual agonist, PPARγ/δ dual agonist and pan-PPAR agonist (i.e. PPARα/γ/δ agonist). Examples of PPARδ agonist include, without limitations, seladelpar or a pharmaceutically acceptable salt thereof. Examples of PPARγ agonist include, without limitations, thiazolidinediones and glitazones, such as pioglitazone, rosiglitazone, rivaglitazone or a pharmaceutically acceptable salt thereof. Examples of PPARα/δ dual agonist include, without limitations, elafibranor or any

pharmaceutically acceptable salts thereof. Examples of PPARα/γ dual agonist include, without limitations, saroglitazar or a pharmaceutically acceptable salt thereof. Examples of pan-PPAR agonist include, without limitations, lanifibranor, chiglitazar or any pharmaceutically acceptable salts thereof. PPAR agonist that are useful in the present invention in combination with a SGLT2 inhibitor include, but are not limited to, PPARα agonist, PPARγ agonist (e.g., pioglitazone, rosiglitazone, rivaglitazone), PPARδ agonist (e.g., seladelpar), PPARα/δ dual agonist, PPARα/γ dual agonist (e.g., elafibranor), PPARγ/δ dual agonist and pan-PPAR agonist (e.g., lanifibranor, chiglitazar). Additional suitable PPAR agonists for use in combination with a SGLT2 inhibitor according to the present invention also include combinations of two or more of the above PPAR agonists or combinations including one or more of the above PPAR agonists with one or more additional compounds.

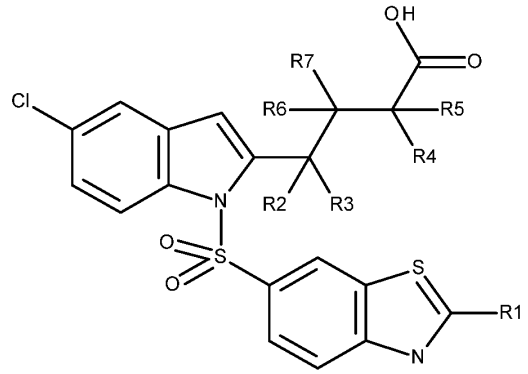
In some embodiments, the PPAR agonist of the invention is a pan-PPAR agonist. Advantageously, the pan-PPAR agonist is selected from the group comprising lanifibranor, a deuterated form of lanifibranor and a pharmaceutically acceptable salt thereof. According to the present invention, lanifibranor or 1-(6-benzothiazolylsulfonyl)-5-chloro-1H-indole-2-butanoic acid is a pan-PPAR agonist with EC_{50s} of 1.5, 0.87 and 0.21 μM for human PPARα, PPARσ and PPARγ, respectively. The chemical formula of lanifibranor is $C_{19}H_{15}ClN_2O_4S_2$, its molecular weight is 434.92 and its CAS Number is 927961-18-0. Lanifibranor 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, and has the following structure:



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In some embodiments, lanifibranor is in crystalline form. Examples of crystalline form of lanifibranor have been described in WO2023/194339, WO2023/016319, WO2022/122014, WO2022/261410 or WO2022/258060, all incorporated herein by reference. According to the present invention, the term "lanifibranor" also includes lanifibranor as described in example 117 of WO 2007/026097, a pharmaceutically acceptable salt of lanifibranor or a solvate of lanifibranor. In some embodiments, the term "lanifibranor" also includes deuterated forms of lanifibranor. As used herein, "deuterated form of lanifibranor" or "deuterated derivative 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. Within the context of the invention, the terms "deuterated form" and "deuterated derivative" are interchangeable. In some embodiments, a deuterated form of lanifibranor is a compound of formula (I):



(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.

Unless otherwise noted, according to this invention it is to be understood that the definitions of the active agents (including SGLT2 inhibitor and PPAR agonist) mentioned hereinbefore and hereinafter may also contemplate their pharmaceutically acceptable salts, and prodrugs, hydrates, solvates and polymorphic forms thereof. Particularly the terms of the therapeutic agents given herein refer to the respective active drugs. With respect to salts, hydrates and polymorphic forms thereof, particular reference is made to those which are referred to herein.

In one aspect, the pharmaceutical compositions and uses according to this disclosure relate to combinations, wherein the SGLT2 inhibitor and the PPAR agonist are each selected as described herein.

In some embodiments, the compositions and uses according to this disclosure relate to combinations, wherein (i) a SGLT2 inhibitor is selected from canaglifozin,

dapagliflozin, remoglifozin, sergliflozin, empagliflozin, ipragliflozin, tofogliflozin, luseogliflozin, sotagliflozin, ertuglifozin, bexagliflozin, henagliflozin, janagliflozin and tianagliflozin; and (ii) a PPAR agonist is selected from PPARα agonist, PPARγ agonist, PPARδ agonist, PPARα/δ dual agonist, PPARα/γ dual agonist, PPARγ/δ dual agonist and PPARα/δ pan-PPAR agonist (i.e PPARα/γ/δ agonist).

In some embodiments, the compositions and uses according to this disclosure relate to combinations wherein the SGLT2 inhibitor and the PPAR agonist are as follows:

SGLT2 inhibitor	**PPAR agonist**
empagliflozin	seladelpar
empagliflozin	pioglitazone,
empagliflozin	rosiglitazone
empagliflozin	rivaglitazone
empagliflozin	elafibranor
empagliflozin	saroglitazar
empagliflozin	lanifibranor
empagliflozin	chiglitazar

In some embodiments, the compositions and uses according to this disclosure relate to combinations, wherein the SGLT2 inhibitor is empagliflozin and the PPAR agonist is lanifibranor.

The aspects according to the present disclosure, in particular the methods and uses, refer to a treatment of patients who have been treated, are treated or are planned to be treated with a PPAR agonist as defined hereinbefore and hereinafter.

According to some embodiments, the patient has been treated with a PPAR agonist. According to some embodiments, the patient is treated with a PPAR agonist. According to some embodiments, the patient is planned to be treated, i.e. will be treated with a PPAR agonist. According to some embodiments, the PPAR agonist is pan-PPAR agonist, in particular with lanifibranor, a deuterated form of lanifibranor or a pharmaceutically acceptable salt of lanifibranor. In some embodiments, the patient has been treated with lanifibranor. In some embodiments, the patient is treated with lanifibranor. In some embodiments, the patient is planned to be treated with lanifibranor. In some embodiments, the patient has been treated with a deuterated form of lanifibranor. In some embodiment, the patient is treated with a deuterated form lanifibranor. In some embodiments, the patient is planned to be treated with a deuterated form lanifibranor. In some embodiments, the patient has been treated with a pharmaceutically acceptable salt of lanifibranor. In some embodiments, the patient is treated with a

pharmaceutically acceptable salt of lanifibranor. In some embodiments, the patient is planned to be treated with a pharmaceutically acceptable salt of lanifibranor.

According to some embodiments of this disclosure, the patient is already under treatment with a PPAR agonist. In some embodiments, the patient is already under treatment with a pan-PPAR agonist, in particular with lanifibranor, a deuterated form of lanifibranor or a pharmaceutically acceptable salt of lanifibranor. In some embodiments, the patient is already under treatment with lanifibranor. In some embodiments, the patient is already under treatment with a deuterated form of lanifibranor. In some embodiments, the patient is already under treatment with a pharmaceutically acceptable salt of lanifibranor.

According to some embodiments of this disclosure, the patient is diagnosed with a liver disease. In some embodiments, the liver disease is selected from cirrhosis, liver fibrosis, liver steatosis, fatty liver disease, acute decompensation, 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), diabetes, autoimmune cholangitis, primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), autoimmune cholangiopathy, hepatocarcinoma (HCC) and a combination of these diseases.

In some embodiments, the liver disease is selected from liver fibrosis, liver steatosis, fatty liver disease, acute decompensation, 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), diabetes, autoimmune cholangitis, primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), autoimmune cholangiopathy, hepatocarcinoma (HCC) and a combination of these diseases. In some embodiments, the patient is diagnosed with metabolic-associated steatohepatitis. In some embodiments, the patient is diagnosed with non-alcoholic steatohepatitis. In some embodiments, the patient is diagnosed with non-alcoholic fatty liver disease. In some embodiments, the patient is diagnosed with metabolic-associated fatty liver disease. In some embodiment, the patient is diagnosed with diabetes, in particular a type 2 diabetes.

In some embodiments, the patient is diagnosed with autoimmune cholangitis. In some embodiments, the patient is diagnosed with primary biliary cholangitis (PBC). In some embodiments, the patient is diagnosed with primary sclerosing cholangitis (PSC). In some embodiments, the patient is diagnosed with autoimmune cholangiopathy. In some embodiments, the patient is diagnosed with hepatocarcinoma (HCC).

In some embodiment, the patient is diagnosed with metabolic-associated steatohepatitis and diabetes, in particular a type 2 diabetes. In some embodiment, the patient is diagnosed with non-alcoholic steatohepatitis and diabetes, in particular a type 2 diabetes. In some embodiment, the patient is diagnosed with non-alcoholic fatty liver disease and diabetes, in particular a type 2 diabetes. In some embodiment, the patient is diagnosed with metabolic-associated fatty liver disease and diabetes, in particular a type 2 diabetes.

In some embodiments, the patient is diagnosed with metabolic-associated steatohepatitis and has been treated, is treated or is planned to be treated with lanifibranor, a deuterated form of lanifibranor or a pharmaceutically acceptable salt of lanifibranor. In some embodiments, the patient is diagnosed with metabolic-associated steatohepatitis and has been treated, is treated or is planned to be treated with lanifibranor.

In some embodiments, the patient is diagnosed with non-alcoholic steatohepatitis and has been treated, is treated or is planned to be treated with lanifibranor, a deuterated form of lanifibranor or a pharmaceutically acceptable salt of lanifibranor. In some embodiments, the patient is diagnosed with non-alcoholic steatohepatitis and has been treated, is treated or is planned to be treated with lanifibranor.

In some embodiments, the patient is diagnosed with non-alcoholic fatty liver disease and has been treated, is treated or is planned to be treated with lanifibranor, a deuterated form of lanifibranor or a pharmaceutically acceptable salt of lanifibranor. In some embodiments, the patient is diagnosed with non-alcoholic fatty liver disease and has been treated, is treated or is planned to be treated with lanifibranor.

In some embodiments, the patient is diagnosed with metabolic-associated fatty liver disease and has been treated, is treated or is planned to be treated with lanifibranor, a deuterated form of lanifibranor or a pharmaceutically acceptable salt of lanifibranor. In some embodiments, the patient is diagnosed with metabolic-associated fatty liver disease and has been treated, is treated or is planned to be treated with lanifibranor.

In some embodiments, the patient is diagnosed with autoimmune cholangitis and has been treated, is treated or is planned to be treated with lanifibranor, a deuterated form of lanifibranor or a pharmaceutically acceptable salt of lanifibranor. In some embodiments, the patient is diagnosed with autoimmune cholangitis and has been treated, is treated or is planned to be treated with lanifibranor. In some embodiments, the patient is diagnosed with primary biliary cholangitis (PBC) and has been treated, is treated or is planned to be treated with lanifibranor, a deuterated form of lanifibranor or a pharmaceutically acceptable salt of lanifibranor. In some embodiments, the patient is diagnosed with primary biliary cholangitis (PBC) and has been treated, is

treated or is planned to be treated with lanifibranor. In some embodiments, the patient is diagnosed with primary sclerosing cholangitis (PSC) and has been treated, is treated or is planned to be treated with lanifibranor, a deuterated form of lanifibranor or a pharmaceutically acceptable salt of lanifibranor. In some embodiments, the patient is diagnosed with primary sclerosing cholangitis (PSC) and has been treated, is treated or is planned to be treated with lanifibranor. In some embodiments, the patient is diagnosed with autoimmune cholangiopathy and has been treated, is treated or is planned to be treated with lanifibranor, a deuterated form of lanifibranor or a pharmaceutically acceptable salt of lanifibranor. In some embodiments, the patient is diagnosed with autoimmune cholangiopathy and has been treated, is treated or is planned to be treated with lanifibranor. In some embodiments, the patient is diagnosed with hepatocarcinoma (HCC) and has been treated, is treated or is planned to be treated with lanifibranor, a deuterated form of lanifibranor or a pharmaceutically acceptable salt of lanifibranor. In some embodiments, the patient is diagnosed with hepatocarcinoma (HCC) and has been treated, is treated or is planned to be treated with lanifibranor.

In some embodiment, the patient who received, receives or will receive a treatment with lanifibranor, a deuterated form of lanifibranor or a pharmaceutically acceptable salt of lanifibranor, is diagnosed with one of the following conditions:

a) metabolic-associated steatohepatitis and type 2 diabetes, or

b) non-alcoholic steatohepatitis and type 2 diabetes, or

c) non-alcoholic fatty liver disease and type 2 diabetes, or

d) metabolic-associated fatty liver disease and type 2 diabetes.

In some embodiment, the patient who received, receives or will receive a treatment with lanifibranor, is diagnosed with one of the following conditions:

a) metabolic-associated steatohepatitis and type 2 diabetes, or

b) non-alcoholic steatohepatitis and type 2 diabetes, or

c) non-alcoholic fatty liver disease and type 2 diabetes, or

d) metabolic-associated fatty liver disease and type 2 diabetes.

In some embodiments of the present disclosure, the patient:

a. is diagnosed with one or more of the conditions selected from the group consisting of overweight, obesity, visceral obesity and abdominal obesity; or

b. displays at least one of the following conditions:

(a) being over the age of 40 years;

(b) a poor iron absorption;

(c) a body mass index equal to or greater than 30 kg/m^2;

(d) a reference amount of HbA1c equal to or greater than 7.0 %;

(e) a reference amount of hemoglobin equal to or lower than 140 g/L;

(f) diagnosed with one of the following diseases: diabetes, dyslipidemia, cardiovascular diseases, cancer, polycystic ovary syndrome, acute lung injury, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, insulin resistance, obesity, diseases linked to endothelial dysfunction, atherosclerosis, myocardial infarction, hypertension, cerebrovascular problems, inflammatory diseases such as rheumatoid arthritis, chronic kidney disease, a pulmonary fibrotic disorder such as idiopathic pulmonary fibrosis, systemic sclerosis and neurodegeneration such as Alzheimer's disease or Parkinson's disease;

(g) diagnosed with a liver disease;

(h) diagnosed with non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), metabolic-associated fatty liver disease (MAFLD), and/or metabolic-associated steatohepatitis (MASH).

In some embodiments, the patient displays at least one of the following conditions:

(a) being over the age of 40 years;

(b) a poor iron absorption;

(c) a body mass index equal to or greater than 30 kg/m^2;

(d) a reference amount of HbA1c equal to or greater than 7.0 %;

(e) a reference amount of hemoglobin equal to or below 140 g/L;

(f) diagnosed with one of the following diseases: diabetes, dyslipidemia, cardiovascular diseases, cancer, polycystic ovary syndrome, acute lung injury, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, insulin resistance, obesity, diseases linked to endothelial dysfunction, atherosclerosis, myocardial infarction, hypertension, cerebrovascular problems, inflammatory diseases such as rheumatoid arthritis, chronic kidney disease, a pulmonary fibrotic disorder such as idiopathic pulmonary fibrosis, systemic sclerosis and neurodegeneration such as Alzheimer's disease or Parkinson's disease;

(g) diagnosed with a liver disease;

(h) diagnosed with non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), metabolic-associated fatty liver disease (MAFLD), and/or metabolic-associated steatohepatitis (MASH).

In some embodiments, the patient is over the age of 40 years. It is known that the frequency of blood disorders increases with age. In some embodiments, the patient is

over the age of 40 years, over the age of 41 years, over the age of 42 years, over the age of 43 years, over the age of 44 years, over the age of 45 years, over the age of 46 years, over the age of 47 years, over the age of 48 years, over the age of 49 years, over the age of 50 years, over the age of 51 years, over the age of 52 years, over the age of 53 years, over the age of 54 years, over the age of 55 years, over the age of 56 years, over the age of 57 years, over the age of 58 years, over the age of 59 years, over the age of 60 years, over the age of 61 years, over the age of 62 years, over the age of 63 years, over the age of 64 years, over the age of 65 years, over the age of 66 years, over the age of 67 years, over the age of 68 years, over the age of 69 years, over the age of 70 years, over the age of 71 years, over the age of 72 years, over the age of 73 years, over the age of 74 years, over the age of 75 years, over the age of 76 years, over the age of 77 years, over the age of 78 years, over the age of 79 years, over the age of 80 years. In especially preferred embodiments, the patient is over the age of 40 years.

In some embodiments, the patient is a male. In some embodiments, the patient is a male and is over the age of 65 years. In some embodiments, the patient is a male and is over the age of 70 years. In some embodiments, the patient is a female. In some embodiments, the patient is a post-menopaused female. In some embodiments, the patient is a female and is over the age of 40 years. In some embodiments of the invention, the patient is a female and is over the age of 50 years. In some embodiments, the patient is a post-menopaused female and is over the age of 50 years. In some embodiments, the patient is a post-menopaused female and is over the age of 60 years.

In some embodiments, the patient displays a poor iron absorption. As used herein, the term "poor iron absorption" means that the iron absorption in the small intestine is less than 1mg per day, for example less than 0.9 mg per day, for example less than 0.8 mg per day, for example less than 0.7 mg per day, for example less than 0.6 mg per day, for example less than 0.5 mg per day, for example less than 0.4 mg per day, for example less than 0.3 mg per day. For instance, iron absorption can be measured by assaying amounts of ferritin. The term "poor iron absorption" also includes the inability to absorb iron.

In some embodiments, the patient displays a reference amount of ferritin greater than or equal to 35 µg/L. In some embodiments, the patient displays a reference amount of ferritin greater than or equal to 36 µg/L, greater than or equal to 37 µg/L, greater than or equal to 38 µg/L, greater than or equal to 39 µg/L, greater than or equal to 40 µg/L, greater than or equal to 41 µg/L, greater than or equal to 42 µg/L, greater than or equal to 43 µg/L, greater than or equal to 44 µg/L, greater than or equal to 45

µg/L, greater than or equal to 46 µg/L, greater than or equal to 47 µg/L, greater than or equal to 48 µg/L, greater than or equal to 49 µg/L, greater than or equal to 50 µg/L, greater than or equal to 51 µg/L, greater than or equal to 52 µg/L, greater than or equal to 53 µg/L, greater than or equal to 54 µg/L, greater than or equal to 55 µg/L, greater than or equal to 56 µg/L, greater than or equal to 57 µg/L, greater than or equal to 58 µg/L, greater than or equal to 59 µg/L, greater than or equal to 60 µg/L, greater than or equal to 61 µg/L, greater than or equal to 62 µg/L, greater than or equal to 63 µg/L, greater than or equal to 64 µg/L, greater than or equal to 65 µg/L, greater than or equal to 66µg/L, greater than or equal to 67 µg/L, greater than or equal to 68 µg/L, greater than or equal to 69 µg/L, greater than or equal to 70 µg/L.

In some embodiments, the patient displays a body mass index equal to or greater than 30 kg/m^2. As used herein, the term "body mass index" or "BMI" of a human patient is defined as the weight in kilograms divided by the square of the height in meters, such that BMI has units of kg/m^2. In some embodiments, the patient has a body mass index equal to or greater than 30.5 kg/m^2, for example a body mass index equal to or greater than 31 kg/m^2, for example a body mass index equal to or greater than 31.5 kg/m^2, for example a body mass index equal to or greater than 32 kg/m^2, for example a body mass index equal to or greater than 32.5 kg/m^2, for example a body mass index equal to or greater than 33 kg/m^2, for example a body mass index equal to or greater than 33.5 $kg/m^{2.}$, for example a body mass index equal to or greater than 34 $kg/m^{2.}$, for example a body mass index equal to or greater than 34.5 kg/m^2, for example a body mass index equal to or greater than 35 kg/m^2, for example a body mass index equal to or greater than 35.5 kg/m^2. In some embodiments, the patient has a body mass index equal to or less than 45 kg/m^2. In some embodiments, the patient has a body mass index comprised between 30 kg/m^2 and 45 kg/m^2. For example, the patient has a body mass index comprised between 31 kg/m^2 and 40 kg/m^2, for example comprised between 31.5 kg/m^2 and 35.5 kg/m^2.

In some embodiments, the patient displays a reference amount of HbA1c equal to or greater than 7.0 %. As used herein, the term "HbA1c" refers to the product of a non-enzymatic glycation of the haemoglobin B chain. Its determination is well known to one skilled in the art. In monitoring the treatment of liver disease, the HbA1c value is of exceptional importance. In some embodiments, the patient displays a reference amount of HbA1c equal to or greater than 7.1%, for example a reference amount of HbA1c equal to or greater than 7.2%, for example a reference amount of HbA1c equal to or greater than 7.3%, for example a reference amount of HbA1c equal to or greater than 7.4%, for example a reference amount of HbA1c equal to or greater than 7.5%,

for example a reference amount of HbA1c equal to or greater than 7.6%, for example a reference amount of HbA1c equal to or greater than 7.7%, for example a reference amount of HbA1c to or greater than 7.8%, for example a reference amount of HbA1c equal to or greater than 7.9%, for example a reference amount of HbA1c equal to or greater than 8.0%, for example a reference amount of HbA1c equal to or greater than 8.1%, for example a reference amount of HbA1c equal to or greater than 8.2%, for example a reference amount of HbA1c equal to or greater than 8.3%, for example a reference amount of HbA1c equal to or greater than 8.4%, for example a reference amount of HbA1c equal to or greater than 8.5%, for example a reference amount of HbA1c to or greater than 8.6%, for example a reference amount of HbA1c equal to or greater than 8.7%, for example a reference amount of HbA1c equal to or greater than 8.9%, for example a reference amount of HbA1c equal to or greater than 9.0%, for example a reference amount of HbA1c equal to or greater than 9.1%, for example a reference amount of HbA1c equal to or greater than 9.2%, for example a reference amount of HbA1c equal to or greater than 9.3%, for example a reference amount of HbA1c equal to or greater than 9.4%, for example a reference amount of HbA1c equal to or greater than 9.5%, for example a reference amount of HbA1c equal to or greater than 9.6%, for example a reference amount of HbA1c equal to or greater than 9.7%, for example a reference amount of HbA1c equal to or greater than 9.8%, for example a reference amount of HbA1c equal to or greater than 9.9%, for example a reference amount of HbA1c equal to or greater than 10.0%. In some embodiments, the patient displays a reference amount of HbA1c comprised between 7.0 % and 10.0%. In some embodiments, the patient displays a reference amount of HbA1c comprised between 7.0% and 9.0%, for example a reference amount of HbA1c comprised between 7.2% and 8.6%.

In some embodiments, the patient has a reference amount of hemoglobin equal to or below than 140 g/L. In some embodiments, the patient has a reference amount of hemoglobin equal to or below than 139 g/L, for example equal to or below than 138 g/L, for example equal to or below than 137 g/L, for example equal to or below than 136 g/L, for example equal to or below than 135 g/L, for example equal to or below than 134 g/L, for example equal to or below than 133 g/L, for example equal to or below than 132 g/L, for example equal to or below than 131 g/L, for example equal to or below than 130 g/L, for example equal to or below than 129 g/L, for example equal to or below than 128 g/L, for example equal to or below than 127 g/L, for example equal to or below than 126 g/L, for example equal to or below than 125 g/L, for example equal to or below than 124 g/L, for example equal to or below than 123 g/L, for example equal to or below than 122 g/L, for example equal to or below than 121

g/L, for example equal to or below than 120 g/L, for example equal to or below than 119 g/L, for example equal to or below 118 g/L, for example equal to or below 117 g/L, for example equal to or below than 116 g/L, for example equal to or below than 115 g/L, for example equal to or below than 114 g/L, for example equal to or below than 113 g/L, for example equal to or below than 112 g/L, for example equal to or below than 111 g/L, for example equal to 110 g/L. In some embodiments, the patient has a reference amount of hemoglobin between 110 g/L and 140 g/L. In some embodiments, the patient has a reference amount of hemoglobin between 111 g/L and 140 g/L. In some embodiments, the patient has a reference amount of hemoglobin between 112 g/L and 140 g/L. In some embodiments, the patient has a reference amount of hemoglobin between 113 g/L and 140 g/L. In some embodiments, the patient has a reference amount of hemoglobin between 114 g/L and 140 g/L. In some embodiments, the patient has a reference amount of hemoglobin between 115 g/L and 140 g/L. In some embodiments, the patient has a reference amount of hemoglobin between 116 g/L and 140 g/L. In some embodiments, the patient has a reference amount of hemoglobin between 117 g/L and 140 g/L. In some embodiments, the patient has a reference amount of hemoglobin between 118 g/L and 140 g/L. In some embodiments, the patient has a reference amount of hemoglobin between 119 g/L and 140 g/L. In some embodiments, the patient has a reference amount of hemoglobin between 120 g/L and 140 g/L. In some embodiments, the patient has a reference amount of hemoglobin between 121 g/L and 140 g/L. In some embodiments, the patient has a reference amount of hemoglobin between 122 g/L and 140 g/L. In some embodiments, the patient has a reference amount of hemoglobin between 123 g/L and 140 g/L. In some embodiments, the patient has a reference amount of hemoglobin between 124 g/L and 140 g/L. In some embodiments, the patient has a reference amount of hemoglobin between 125 g/L and 140 g/L. In some embodiments, the patient has a reference amount of hemoglobin between 126 g/L and 140 g/L. In some embodiments, the patient has a reference amount of hemoglobin between 127 g/L and 140 g/L. In some embodiments, the patient has a reference amount of hemoglobin between 128 g/L and 140 g/L. In some embodiments, the patient has a reference amount of hemoglobin between 129 g/L and 140 g/L. In some embodiments, the patient has a reference amount of hemoglobin between 130 g/L and 140 g/L. In some embodiments, the patient has a reference amount of hemoglobin equal to or below than 140 g/L. In some embodiments, the patient has a reference amount of hemoglobin between 131 g/L and 140 g/L. In some embodiments, the patient has a reference amount of hemoglobin between 132 g/L and 140 g/L. In some embodiments, the patient has a reference amount of hemoglobin between 133 g/L and

140 g/L. In some embodiments, the patient has a reference amount of hemoglobin between 134 g/L and 140 g/L. In some embodiments, the patient has a reference amount of hemoglobin between 135 g/L and 140 g/L. In some embodiments, the patient has a reference amount of hemoglobin between 136 g/L and 140 g/L. In some embodiments, the patient has a reference amount of hemoglobin between 137 g/L and 140 g/L. In some embodiments, the patient has a reference amount of hemoglobin between 138 g/L and 140 g/L. In some embodiments, the patient has a reference amount of hemoglobin between 139 g/L and 140 g/L. In some embodiments, the patient has a reference amount of hemoglobin equal to or below than 132 g/L. In some embodiments, the patient has a reference amount of hemoglobin equal to or below 120 g/L. In some embodiments, the patient has a reference amount of hemoglobin equal to or below than 119 g/L. In some embodiments, the patient has a reference amount of hemoglobin equal to or below than 118 g/L. In some embodiments, the patient has a reference amount of hemoglobin equal to or below than 115 g/L.

In some embodiments, the patient is diagnosed with one of the following diseases: diabetes, dyslipidemia, cardiovascular diseases, cancer, polycystic ovary syndrome, acute lung injury, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, insulin resistance, obesity, diseases linked to endothelial dysfunction, atherosclerosis, myocardial infarction, hypertension, cerebrovascular problems, inflammatory diseases such as rheumatoid arthritis, chronic kidney disease, a pulmonary fibrotic disorder such as idiopathic pulmonary fibrosis, systemic sclerosis and neurodegeneration such as Alzheimer's disease or Parkinson's disease.

In some embodiments, the patient is diagnosed with one or more of the conditions selected from the group consisting of overweight, obesity, visceral obesity and abdominal obesity. In some embodiments, the patient is diagnosed as being overweight or obese, including class I, II and/or III obesity, or with visceral obesity and/or abdominal obesity.

As used herein, the term "overweight" is defined as the condition wherein the individual has a BMI greater than 25 kg/m^2 and less than 30 kg/m^2. As used herein, the term "obesity" is defined as the condition wherein the individual has a BMI equal to or greater than 30 kg/m^2. According to a WHO definition the term obesity may be categorized as follows: the term "class I obesity" is the condition wherein the BMI is equal to or greater than 30 kg/m^2 but lower than 35 kg/m^2; the term "class II obesity" is the condition wherein the BMI is equal to or greater than 35 kg/m^2 but lower than 40 kg/m^2; the term "class III obesity" is the condition wherein the BMI is equal to or greater than 40 kg/m^2. As used herein, the term "visceral obesity" is defined as the

condition wherein a waist-to-hip ratio of greater than or equal to 1.0 in men and 0.8 in women is measured. As used herein, the term "abdominal obesity" is usually defined as the condition wherein the waist circumference is greater than 102 cm in men, and is greater than 94 cm in women.

In some embodiments, the patient is diagnosed with at least one of the following diseases: non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), metabolic-associated fatty liver disease (MAFLD), and metabolic-associated steatohepatitis (MASH), visceral obesity and/or abdominal obesity. In some embodiments, the patient is diagnosed with non-alcoholic fatty liver disease (NAFLD). In some embodiments, the patient is diagnosed with non-alcoholic steatohepatitis (NASH). In some embodiments, the patient is diagnosed with metabolic-associated fatty liver disease (MAFLD). In some embodiments, the patient is diagnosed with metabolic-associated steatohepatitis (MASH). In some embodiments, the patient is diagnosed with diagnosed for visceral obesity. In some embodiments, the patient is diagnosed with abdominal obesity. In some embodiments, the patient is diagnosed with visceral obesity and abdominal obesity.

In some embodiments, the patient displays at least two, at least three, at least four, at least five, at least six, at least seven or at least eight of the following conditions:

(a) being over the age of 40 years;

(b) a poor iron absorption;

(c) a body mass index equal to or greater than 30 kg/m^2;

(d) a reference amount of HbA1c equal to or greater than 7.0 %;

(e) a reference amount of hemoglobin equal to or below 140 g/L;

(f) diagnosed with one of the following diseases: diabetes, dyslipidemia, cardiovascular diseases, cancer, polycystic ovary syndrome, acute lung injury, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, insulin resistance, obesity, diseases linked to endothelial dysfunction, atherosclerosis, myocardial infarction, hypertension, cerebrovascular problems, inflammatory diseases such as rheumatoid arthritis, chronic kidney disease, a pulmonary fibrotic disorder such as idiopathic pulmonary fibrosis, systemic sclerosis and neurodegeneration such as Alzheimer's disease or Parkinson's disease;

(g) diagnosed with a liver disease;

(h) diagnosed with non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), metabolic-associated fatty liver disease (MAFLD), and/or metabolic-associated steatohepatitis (MASH).

In some embodiments, the patient displays one, two, three, four, five, six, seven or eight of the following conditions:

(a) being over the age of 40 years;

(b) a poor iron absorption;

(c) a body mass index equal to or greater than 30 kg/m^2;

(d) a reference amount of HbA1c equal to or greater than 7.0 %;

(e) a reference amount of hemoglobin equal to or below 140 g/L;

(f) diagnosed with one of the following diseases: diabetes, dyslipidemia, cardiovascular diseases, cancer, polycystic ovary syndrome, acute lung injury, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, insulin resistance, obesity, diseases linked to endothelial dysfunction, atherosclerosis, myocardial infarction, hypertension, cerebrovascular problems, inflammatory diseases such as rheumatoid arthritis, chronic kidney disease, a pulmonary fibrotic disorder such as idiopathic pulmonary fibrosis, systemic sclerosis and neurodegeneration such as Alzheimer's disease or Parkinson's disease;

(g) diagnosed with a liver disease;

(h) diagnosed with non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), metabolic-associated fatty liver disease (MAFLD), and/or metabolic-associated steatohepatitis (MASH).

In some embodiments, the patient further displays at least one of the following conditions:

a. aspartate aminotransferase (AST) amount greater than or equal to 10 U/L;

b. alanine aminotransferase (ALT) amount greater than or equal to 10 U/L;

c. gamma glutamyl transferase (GGT) amount greater than or equal to 3 U/L;

d. fasting blood glucose amount greater than or equal to 4 mmol/L;

e. HDL-cholesterol blood amount below than or equal to 2.50 mmol/L;

f. triglyceride blood amount greater than or equal to 0.70 mmol/L;

g. ferritin amount greater than or equal to 6 µg/L;

h. a systolic blood pressure greater than or equal to 95 mm Hg and a diastolic blood pressure greater than or equal to 60 mm Hg;

i. ratio visceral adipose tissue (VAT)/ subcutaneous adipose tissue (SAT) (VAT/SAT) greater than or equal to 0.30;

j. cT1 amount greater than or equal to 700 ms.

In some embodiments, the patient displays at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least elven or at least twelve of the following conditions:

a. aspartate aminotransferase (AST) amount greater than or equal to 10 U/L;
b. alanine aminotransferase (ALT) amount greater than or equal to 10 U/L;
c. gamma glutamyl transferase (GGT) amount greater than or equal to 3 U/L;
d. fasting blood glucose amount greater than or equal to 4 mmol/L;
e. HDL-cholesterol blood amount below than or equal to 2.50 mmol/L;
f. triglyceride blood amount greater than or equal to 0.70 mmol/L;
g. ferritin amount greater than or equal to 6 µg/L;
h. a systolic blood pressure greater than or equal to 95 mm Hg and a diastolic blood pressure greater than or equal to 60 mm Hg;
i. ratio visceral adipose tissue (VAT)/ subcutaneous adipose tissue (SAT) (VAT/SAT) greater than or equal to 0.30;
j. cT1 amount greater than or equal to 700 ms.

In some embodiments, the patient displays one, two, three, four, five, six, seven, eight, nine, ten, elven or twelve of the following conditions:

a. aspartate aminotransferase (AST) amount greater than or equal to 10 U/L;
b. alanine aminotransferase (ALT) amount greater than or equal to 10 U/L;
c. gamma glutamyl transferase (GGT) amount greater than or equal to 3 U/L;
d. fasting blood glucose amount greater than or equal to 4 mmol/L;
e. HDL-cholesterol blood amount below than or equal to 2.50 mmol/L;
f. triglyceride blood amount greater than or equal to 0.70 mmol/L;
g. ferritin amount greater than or equal to 6 µg/L;
h. a systolic blood pressure greater than or equal to 95 mm Hg and a diastolic blood pressure greater than or equal to 60 mm Hg;
i. ratio visceral adipose tissue (VAT)/subcutaneous adipose tissue (SAT) (VAT/SAT) greater than or equal to 0.30;
j. cT1 amount greater than or equal to 700 ms.

In some embodiments, the aspartate aminotransferase (AST) amount is greater than or equal to 10 U/L, greater than or equal to 15 U/L, greater than or equal to 20 U/L, greater than or equal to 25 U/L, greater than or equal to 30 U/L, greater than or equal to 35 U/L, greater than or equal to 40 U/L, greater than or equal to 45 U/L, greater than or equal to 50 U/L, greater than or equal to 55 U/L, greater than or equal to 60 U/L, greater than or equal to 65 U/L, greater than or equal to 70 U/L, greater than or equal to 75 U/L, greater than or equal to 80 U/L , greater than or equal to 85 U/L, greater than or equal to 90 U/L, greater than or equal to 95 U/L, greater than or equal to 100 U/L, greater than or equal to 105 U/L, greater than or equal to 110 U/L.

In some embodiments, the alanine aminotransferase (ALT) amount is greater than or equal to 10 U/L, greater than or equal to 15 U/L, greater than or equal to 20 U/L,

greater than or equal to 25 U/L, greater than or equal to 30 U/L, greater than or equal to 35 U/L, greater than or equal to 40 U/L, greater than or equal to 45 U/L, greater than or equal to 50 U/L, greater than or equal to 55 U/L, greater than or equal to 60 U/L, greater than or equal to 65 U/L, greater than or equal to 70 U/L, greater than or equal to 75 U/L, greater than or equal to 80 U/L , greater than or equal to 85 U/L, greater than or equal to 90 U/L, greater than or equal to 95 U/L, greater than or equal to 100 U/L, greater than or equal to 105 U/L, greater than or equal to 110 U/L, greater than or equal to 115 U/L, greater than or equal to 120 U/L, greater than or equal to 125 U/L, greater than or equal to 130 U/L, greater than or equal to 135 U/L, greater than or equal to 140 U/L, greater than or equal to 145 U/L, greater than or equal to 150 U/L, greater than or equal to 155 U/L, greater than or equal to 160 U/L, greater than or equal to 165 U/L, greater than or equal to 170 U/L, greater than or equal to 175 U/L, greater than or equal to 180 U/L.

In some embodiments, the gamma glutamyl transferase (GGT) amount is greater than or equal to 3 U/L, greater than or equal to 4 U/L, greater than or equal to 5 U/L, greater than or equal to 6 U/L, greater than or equal to 7 U/L, greater than or equal to 8 U/L, greater than or equal to 9 U/L, greater than or equal to 10 U/L, greater than or equal to 15 U/L, greater than or equal to 20 U/L, greater than or equal to 25 U/L, greater than or equal to 30 U/L, greater than or equal to 35 U/L, greater than or equal to 40 U/L, greater than or equal to 45 U/L, greater than or equal to 50 U/L, greater than or equal to 55 U/L, greater than or equal to 60 U/L, greater than or equal to 65 U/L, greater than or equal to 70 U/L, greater than or equal to 75 U/L, greater than or equal to 80 U/L , greater than or equal to 85 U/L, greater than or equal to 90 U/L, greater than or equal to 95 U/L, greater than or equal to 100 U/L, greater than or equal to 105 U/L, greater than or equal to 110 U/L, greater than or equal to 115 U/L, greater than or equal to 120 U/L, greater than or equal to 125 U/L, greater than or equal to 130 U/L, greater than or equal to 135 U/L, greater than or equal to 140 U/L, greater than or equal to 145 U/L, greater than or equal to 150 U/L, greater than or equal to 155 U/L, greater than or equal to 160 U/L, greater than or equal to 165 U/L, greater than or equal to 170 U/L, greater than or equal to 175 U/L, greater than or equal to 180 U/L, greater than or equal to 190 U/L, greater than or equal to 195 U/L, greater than or equal to 200 U/L greater, than or equal to 210 U/L, greater than or equal to 215 U/L, greater than or equal to 220 U/L, greater than or equal to 225 U/L, greater than or equal to 230 U/L, greater than or equal to 235 U/L, greater than or equal to 240 U/L, greater than or equal to 245 U/L, greater than or equal to 250 U/L, greater than or equal to 255 U/L, greater than or equal to 260 U/L, greater than or equal to 265 U/L, greater than or equal to 270 U/L, greater than or equal to 275 U/L,

greater than or equal to 280 U/L, greater than or equal to 285 U/L, greater than or equal to 290 U/L, greater than or equal to 295 U/L, greater than or equal to 300 U/L, greater than or equal to 310 U/L, greater than or equal to 315 U/L, greater than or equal to 320 U/L, greater than or equal to 325 U/L, greater than or equal to 330 U/L, greater than or equal to 335 U/L, greater than or equal to 340 U/L, greater than or equal to 345 U/L, greater than or equal to 350 U/L, greater than or equal to 355 U/L, greater than or equal to 360 U/L, greater than or equal to 365 U/L, greater than or equal to 370 U/L.

In some embodiments, the fasting blood glucose amount is greater than or equal to 4.0 mmol/L, greater than or equal to 4.5 mmol/L, greater than or equal to 5.0 mmol/L, greater than or equal to 5.5 mmol/L, greater than or equal to 6.0 mmol/L, greater than or equal to 6.5 mmol/L, greater than or equal to 7.0 mmol/L, greater than or equal to 7.5 mmol/L, greater than or equal to 8.0 mmol/L, greater than or equal to 8.5 mmol/L, greater than or equal to 9.0 mmol/L, greater than or equal to 9.5 mmol/L, greater than or equal to 10.0 mmol/L, greater than or equal to 10.1 mmol/L, greater than or equal to 10.2 mmol/L, greater than or equal to 10.3 mmol/L, greater than or equal to 10.4 mmol/L, greater than or equal to 10.5 mmol/L.

In some embodiments, the HDL-cholesterol blood amount is below than or equal to 2.50 mmol/L, below than or equal to 2.00 mmol/L, below than or equal to 1.90 mmol/L, below than or equal to 1.80 mmol/L, below than or equal to 1.70 mmol/L, below than or equal to 1.60 mmol/L, below than or equal to 1.50 mmol/L, below than or equal to 1.40 mmol/L, below than or equal to 1.30 mmol/L, greater than or equal to 1.20 mmol/L, below than or equal to 1.10 mmol/L, below than or equal to 1.0 mmol/L, below than or equal to 0.90 mmol/L, below than or equal to 0.85 mmol/L, below than or equal to 0.80 mmol/L, below than or equal to 0.75 mmol/L, below than or equal to 0.70 mmol/L, below than or equal to 0.65 mmol/L below than or equal to 0.60 mmol/L, below than or equal to 0.55 mmol/L, below than or equal to 0.50 mmol/L.

In some embodiments, the triglyceride blood amount is greater than or equal to 0.70 mmol/L, greater than or equal to 0.80 mmol/L, greater than or equal to 0.90 mmol/L, greater than or equal to 1.00 mmol/L, greater than or equal to 1.10 mmol/L, greater than or equal to 1.20 mmol/L, greater than or equal to 1.30 mmol/L, greater than or equal to 1.40 mmol/L, greater than or equal to 1.50 mmol/L, greater than or equal to 1.60 mmol/L, greater than or equal to 1.70 mmol/L, greater than or equal to 1.80 mmol/L, greater than or equal to 1.90 mmol/L, greater than or equal to 2.00 mmol/L, greater than or equal to 2.50 mmol/L, greater than or equal to 3.00 mmol/L, greater than or equal to 3.50 mmol/L, greater than or equal to 4.00 mmol/L, greater than or

equal to 4.50 mmol/L, greater than or equal to 5.00 mmol/L, greater than or equal to 5.50 mmol/L, greater than or equal to 6.00 mmol/L, greater than or equal to 6.50 mmol/L, greater than or equal to 7.00 mmol/L, greater than or equal to 7.50 mmol/L, greater than or equal to 8.00 mmol/L, greater than or equal to 8.50 mmol/L, greater than or equal to 9.00 mmol/L, greater than or equal to 9.50 mmol/L, greater than or equal to 10.00 mmol/L, greater than or equal to 10.50 mmol/L, greater than or equal to 11.00 mmol/L, greater than or equal to 11.50 mmol/L, greater than or equal to 12.00 mmol/L, greater than or equal to 12.50 mmol/L, greater than or equal to 13.00 mmol/L, greater than or equal to 13.50 mmol/L, greater than or equal to 14.00 mmol/L, greater than or equal to 14.50 mmol/L, greater than or equal to 15.00 mmol/L, greater than or equal to 15.50 mmol/L, greater than or equal to 16.00 mmol/L, greater than or equal to 16.50 mmol/L, greater than or equal to 17.00 mmol/L, greater than or equal to 17.50 mmol/L, greater than or equal to 18.00 mmol/L, greater than or equal to 18.50 mmol/L, greater than or equal to 19.00 mmol/L, greater than or equal to 19.50 mmol/L, greater than or equal to 20.00 mmol/L, greater than or equal to 20.50 mmol/L, greater than or equal to 21.00 mmol/L, greater than or equal to 21.50 mmol/L, greater than or equal to 22.00 mmol/L, greater than or equal to 22.50 mmol/L, greater than or equal to 23.00 mmol/L, greater than or equal to 23.50 mmol/L, greater than or equal to 24.00 mmol/L, greater than or equal to 24.50 mmol/L, greater than or equal to 25.00 mmol/L, greater than or equal to 25.50 mmol/L, greater than or equal to 26.00 mmol/L, greater than or equal to 26.50 mmol/L, greater than or equal to 27.00 mmol/L, greater than or equal to 27.50 mmol/L, greater than or equal to 28.00 mmol/L, greater than or equal to 28.50 mmol/L, greater than or equal to 29.00 mmol/L, greater than or equal to 29.50 mmol/L, greater than or equal to 30.00 mmol/L.

In some embodiments, the ferritin amount is greater than or equal to 6 µg/L, greater than or equal to 10 µg/L, greater than or equal to 20 µg/L, greater than or equal to 30 µg/L, greater than or equal to 40 µg/L, greater than or equal to 50 µg/L, greater than or equal to 60 µg/L, greater than or equal to 70 µg/L, greater than or equal to 80 µg/L, greater than or equal to 90 µg/L, greater than or equal to 100 µg/L, greater than or equal to 110 µg/L, greater than or equal to 120 µg/L, greater than or equal to 130 µg/L, greater than or equal to 140 µg/L, greater than or equal to 150 µg/L, greater than or equal to 160 µg/L, greater than or equal to 170 µg/L, greater than or equal to 180 µg/L, greater than or equal to 190 µg/L, greater than or equal to 200 µg/L, greater than or equal to 210 µg/L, greater than or equal to 220 µg/L, greater than or equal to 230 µg/L, greater than or equal to 240 µg/L, greater than or equal to

250 µg/L, greater than or equal to 260 µg/L, greater than or equal to 270 µg/L, greater than or equal to 280 µg/L, greater than or equal to 290 µg/L, greater than or equal to 300 µg/L, greater than or equal to 310 µg/L, greater than or equal to 320 µg/L, greater than or equal to 330 µg/L, greater than or equal to 340 µg/L, greater than or equal to 350 µg/L.

In one embodiment, the systolic blood pressure is greater than or equal to 95 mm Hg, greater than or equal to 100 mm Hg, greater than or equal to 105 mm Hg, greater than or equal to 110 mm Hg, greater than or equal to 115 mm Hg, greater than or equal to 120 mm Hg, greater than or equal to 125 mm Hg, greater than or equal to 130 mm Hg, greater than or equal to 135 mm Hg, greater than or equal to 140 mm Hg, greater than or equal to 145 mm Hg, greater than or equal to 150 mm Hg, greater than or equal to 155 mm Hg, greater than or equal to 160 mm Hg, greater than or equal to 165 mm Hg, greater than or equal to 170 mm Hg, greater than or equal to 175 mm Hg, greater than or equal to 180 mm Hg, greater than or equal to 185 mm Hg, greater than or equal to 190 mm Hg. In some embodiments, the diastolic blood pressure is greater than or equal to 60 mm Hg, greater than or equal to 65 mm Hg, greater than or equal to 70 mm Hg, greater than or equal to 75 mm Hg, greater than or equal to 80 mm Hg, greater than or equal to 85 mm Hg, greater than or equal to 90 mm Hg, greater than or equal to 95 mm Hg.

In some embodiments, the ratio VAT/SAT is greater than or equal to 0.30, greater than or equal to 0.40, greater than or equal to 0.50, greater than or equal to 0.60, greater than or equal to 0.70, greater than or equal to 0.80, greater than or equal to 0.90, greater than or equal to 1.0, greater than or equal to 1.1, greater than or equal to 1.2, greater than or equal to 1.3, greater than or equal to 1.4, greater than or equal to 1.5, greater than or equal to 1.6, greater than or equal to 1.7, greater than or equal to 1.8, greater than or equal to 1.9, greater than or equal to 2.0, greater than or equal to 2.1, greater than or equal to 2.2, greater than or equal to 2.3, greater than or equal to 2.4, greater than or equal to 2.5, greater than or equal to 2.6, greater than or equal to 2.7, greater than or equal to 2.8, greater than or equal to 2.9, greater than or equal to 3.0, greater than or equal to 3.1, greater than or equal to 3.2, greater than or equal to 3.3, greater than or equal to 3.4, greater than or equal to 3.5.

In some embodiments, cT1 amount is greater than or equal to 700 ms, greater than or equal to 750 ms, greater than or equal to 800 ms, greater than or equal to 850 ms, greater than or equal to 900 ms, greater than or equal to 950 ms, greater than or equal to 1000 ms, greater than or equal to 1050 ms, greater than or equal to 1100 ms.

In the following, preferred ranges of suitable dosage of the SGLT2 inhibitor and the PPAR agonist to be employed in the pharmaceutical composition and the methods and uses according to this disclosure are described. These ranges refer to the amounts to be administered per day with respect to an adult patient, in particular to a human being, for example of approximately 70 kg body weight, and can be adapted accordingly with regard to an administration 1 or 2 times daily and with regard to other routes of administration and with regard to the age of the patient. The ranges of the dosage and amounts are calculated for the individual active moiety.

The dosage of the SGLT2 inhibitor is from about 0.5 mg to about 1000 mg, for example from about 0.5 mg to about 500 mg, for example from about 0.5 mg to about 200 mg, for example from about 1 to about 100 mg, for example from about 1 to about 50 mg, for example from about 1 to about 25 mg per day. The oral administration is preferred. Therefore, a dosage form for the SGLT2 inhibitor may comprise the hereinbefore mentioned amounts, in particular from about 1 to about 50 mg or about 1 to about 25 mg. Particular dosage strengths (e.g. per tablet or capsule) are for example 1, 2.5, 5, 7.5, 10, 12.5, 15, 20, 25 or 50 mg of the SGLT2 inhibitor. The administration of the SGLT2 inhibitor may occur one, two or three times a day, preferably once a day.

Typical dosages for dapagliflozin are 1 mg, 2.5 mg, 5 mg and 10 mg once daily, and 2.5 mg and 5 mg twice daily. Typical dosages for canagliflozin are 100 mg and 300 mg once daily, or 50 mg or 150 mg twice daily. Typical dosage of empagliflozin is from about 1 to about 50 mg, even more advantageously from about 2.5 to about 25 mg, even more advantageously about 5 to about 25 mg for once daily administration. Advantageous dosages of empagliflozin are for example 2 mg, 2.5 mg, 5 mg, 10 mg, 12.5 mg, 15 mg, 20 mg and 25 mg for once daily administration. Most advantageous dosages of empagliflozin are 10 mg and 25 mg for once daily administration. Advantageously, empagliflozin is administered to the patient with food, advantageously during meal, advantageously during breakfast.

A minimum dosage for the PPAR agonist will vary depending upon the choice of PPAR agonist, but is typically of about 4 mg per day for glitazones or about 80 mg per day for PPARα/δ dual agonist or about 400 mg per day for pan-PPAR agonist. A maximum dosage is about 45 mg per day for glitazones or about 120 mg per day for PPARα/δ dual agonist or about 1200 mg per day for pan-PPAR agonist.

The dosage of the PPAR agonist is from about 4 mg to about 1200 mg per day.

The PPAR agonist is administered one to three times daily, preferably once or twice a day, and especially once a day.

In some embodiments, the PPAR agonist is a pan-PPAR agonist. Advantageously, the pan-PPAR agonist is lanifibranor, a deuterated form of lanifibranor or a pharmaceutically acceptable salt thereof. When the pan-PPAR agonist is lanifibranor, a deuterated form of lanifibranor or a pharmaceutically acceptable salt thereof, the minimum dosage is 400 mg per day, and the maximum dosage is 1200 mg per day. Advantageously, the daily dosages of lanifibranor are for example 400, 500, 600, 700, 800, 900, 1000, 1100, 1200 mg. Advantageously, the dosages of lanifibranor are for example 400, 500, 600, 700, 800, 900, 1000, 1100, 1200 mg per day. The same dosages applied for a deuterated form of lanifibranor or a pharmaceutically acceptable salt of lanifibranor. Advantageously, the dosages of deuterated form of lanifibranor or a pharmaceutically acceptable salt of lanifibranor are for example 400, 500, 600, 700, 800, 900, 1000, 1100, 1200 mg. Advantageously, the dosages of deuterated form of lanifibranor or a pharmaceutically acceptable salt of lanifibranor are for example 400, 500, 600, 700, 800, 900, 1000, 1100, 1200 mg per day.

According to some embodiments, the prevention comprises the administration in combination or alternation or sequentially of the PPAR agonist and the SGLT2 inhibitor. According to some embodiments, the PPAR agonist and the SGLT2 inhibitor are administered in combination or alternation or sequentially. The term "administration in combination" means that the active ingredients are administered at the same time, i.e. simultaneously, or essentially at the same time. The term "administration in alternation" means that at first one of the two active ingredients, i.e. the SGLT2 inhibitor or the PPAR agonist, is administered and after a period of time the other active ingredient, i.e. the PPAR agonist or the SGLT2 inhibitor, is administered whereby this administration scheme may be repeated one or more times. The period of time between the administration of the first and of the second active ingredient may be in the range from 1 min to 12 hours. The administration which is in combination or in alternation may be once, twice, three times or four times daily, preferably once or twice daily. The term "sequentially" means that the first active ingredient, in particular the PPAR agonist, is administered to the patient one or more times in a first period of time followed by an administration of the second active ingredient, in particular the SGLT2 inhibitor which is administered to the patient one or more times in a second period of time. In other words, the term "sequentially" includes a first therapy, in particular with the PPAR agonist, in a first period of time followed by a second therapy, in particular with the SGLT2 inhibitor, in a second period of time.

In some embodiments, when the PPAR agonist is selected from lanifibranor, a deuterated form of lanifibranor and a pharmaceutically acceptable salt thereof, and

when SGLT2 inhibitor is empagliflozin, (i) lanifibranor, a deuterated form of lanifibranor and a pharmaceutically acceptable salt thereof and (ii) empagliflozin are administered in combination or alternation or sequentially. In some embodiments, (i) lanifibranor, a deuterated form of lanifibranor and a pharmaceutically acceptable salt thereof and (ii) empagliflozin are administered in combination. In some embodiments, (i) lanifibranor, a deuterated form of lanifibranor and a pharmaceutically acceptable salt thereof and (ii) empagliflozin are administered in alternation. In some embodiments, (i) lanifibranor, a deuterated form of lanifibranor and a pharmaceutically acceptable salt thereof and (ii) empagliflozin are administered sequentially. In some embodiments, lanifibranor and empagliflozin are administered in combination. In some embodiments, lanifibranor and empagliflozin are administered in alternation. In some embodiments, lanifibranor and (ii) empagliflozin are administered sequentially.

In some embodiments, the first dose of SGLT2 inhibitor is administered to the patient at least one day after the start of the treatment with the PPAR agonist. In some embodiments, the first dose of SGLT2 inhibitor is administered to the patient at least one day, for example at least 2 days, for example at least 3 days, for example at least 4 days, for example at least 5 days, for example at least 6 days, for example at least 7 days, for example at least 8 days, for example at least 9 days, for example at least 10 days, for example at least 11 days, for example at least 12 days, for example at least 13 days, for example at least 14 days, for example at least 15 days, for example at least 16 days, for example at least 17 days, for example at least 18 days, for example at least 19 days, for example at least 20 days, for example at least 21 days, for example at least 22 days, for example at least 23 days, for example at least 24 days, for example at least 25 days, for example at least 26 days, for example at least 27 days, for example at least 28 days, for example at least 29 days, for example at least 30 days, for example at least 31 days, for example at least 1 week, for example at least 2 weeks, for example at least 3 weeks, for example at least 4 weeks, for example at least 5 weeks, for example at least 1 month, for example at least 2 months, for example at least 3 months, for example at least 4 months, for example at least 5 months after the start of the treatment with the PPAR agonist.

In some embodiments, the first dose of SGLT2 inhibitor is administered to the patient at the same time as the first dose of PPAR agonist.

In some embodiments, the first dose of SGLT2 inhibitor is administered to the patient at least one day before the start of the treatment with a PPAR agonist. In some embodiments, the first dose of SGLT2 inhibitor is administered to the patient at least one day, for example at least 2 days, for example at least 3 days, for example at least

4 days, for example at least 5 days, for example at least 6 days, for example at least 7 days, for example at least 8 days, for example at least 9 days, for example at least 10 days, for example at least 11 days, for example at least 12 days, for example at least 13 days, for example at least 14 days, for example at least 15 days, for example at least 16 days, for example at least 17 days, for example at least 18 days, for example at least 19 days, for example at least 20 days, for example at least 21 days, for example at least 22 days, for example at least 23 days, for example at least 24 days, for example at least 25 days, for example at least 26 days, for example at least 27 days, for example at least 28 days, for example at least 29 days, for example at least 30 days, for example at least 31 days, for example at least 1 week, for example at least 2 weeks, for example at least 3 weeks, for example at least 4 weeks, for example at least 5 weeks, for example at least 1 month, for example at least 2 months, for example at least 3 months, for example at least 4 months, for example at least 5 months before the start of the treatment with the PPAR agonist.

In some embodiments, the first dose of empagliflozin is administered to the patient at least one day after the start of the treatment with lanifibranor. In some embodiments, the first dose of empagliflozin is administered to the patient at least one day, for example at least 2 days, for example at least 3 days, for example at least 4 days, for example at least 5 days, for example at least 6 days, for example at least 7 days, for example at least 8 days, for example at least 9 days, for example at least 10 days, for example at least 11 days, for example at least 12 days, for example at least 13 days, for example at least 14 days, for example at least 15 days, for example at least 16 days, for example at least 17 days, for example at least 18 days, for example at least 19 days, for example at least 20 days, for example at least 21 days, for example at least 22 days, for example at least 23 days, for example at least 24 days, for example at least 25 days, for example at least 26 days, for example at least 27 days, for example at least 28 days, for example at least 29 days, for example at least 30 days, for example at least 31 days, for example at least 1 week, for example at least 2 weeks, for example at least 3 weeks, for example at least 4 weeks, for example at least 5 weeks, for example at least 1 month, for example at least 2 months, for example at least 3 months, for example at least 4 months, for example at least 5 months after the start of the treatment with lanifibranor.

In some embodiments, the first dose of empagliflozin is administered to the patient at the same time as the first dose of lanifibranor.

In some embodiments, the first dose of empagliflozin is administered to the patient at least one day before the start of the treatment with lanifibranor. In some embodiments, the first dose of empagliflozin is administered to the patient at least

one day, for example at least 2 days, for example at least 3 days, for example at least 4 days, for example at least 5 days, for example at least 6 days, for example at least 7 days, for example at least 8 days, for example at least 9 days, for example at least 10 days, for example at least 11 days, for example at least 12 days, for example at least 13 days, for example at least 14 days, for example at least 15 days, for example at least 16 days, for example at least 17 days, for example at least 18 days, for example at least 19 days, for example at least 20 days, for example at least 21 days, for example at least 22 days, for example at least 23 days, for example at least 24 days, for example at least 25 days, for example at least 26 days, for example at least 27 days, for example at least 28 days, for example at least 29 days, for example at least 30 days, for example at least 31 days, for example at least 1 week, for example at least 2 weeks, for example at least 3 weeks, for example at least 4 weeks, for example at least 5 weeks, for example at least 1 month, for example at least 2 months, for example at least 3 months, for example at least 4 months, for example at least 5 months before the start of the treatment with lanifibranor.

In some embodiments, the SGLT2 inhibitor is particularly suitable to prevent or delay clinical complications of blood disorders in a patient having been treated, treated or planned to be treated with a PPAR agonist. Advantageously, the SGLT2 inhibitor is particularly suitable in the long-term prevention or delaying of clinical complications of blood disorders in a patient who having been treated, is treated or is planned to be treated with a PPAR agonist. The term "long term" as used hereinbefore and hereinafter indicates a treatment of or administration in a patient within a period of time longer than 4 weeks, advantageously longer than 5 weeks, advantageously longer than 6 weeks, advantageously longer than 7 weeks, advantageously longer than 8 weeks, advantageously longer than 9 weeks, advantageously longer than 10 weeks, advantageously longer than 11 weeks, advantageously longer than 12 weeks, advantageously longer than 13 weeks, advantageously longer than 14 weeks, advantageously longer than 15 weeks, advantageously longer than 16 weeks, advantageously longer than 17 weeks, advantageously longer than 18 weeks, advantageously longer than 19 weeks, advantageously longer than 20 weeks, advantageously longer than 21 weeks, advantageously longer than 22 weeks, advantageously longer than 23 weeks, advantageously longer than 24 weeks, advantageously longer than 25 weeks, advantageously longer than 26 weeks, advantageously longer than 27 weeks, advantageously longer than 28 weeks, advantageously longer than 29 weeks, advantageously longer than 30 weeks, advantageously longer than 31 weeks, advantageously longer than 32 weeks, advantageously longer than 33 weeks, advantageously longer than 34 weeks,

advantageously longer than 35 weeks, advantageously longer than 36 weeks, advantageously longer than 37 weeks, advantageously longer than 38 weeks, advantageously longer than 39 weeks, advantageously longer than 40 weeks, advantageously longer than 41 weeks, advantageously longer than 42 weeks, advantageously longer than 43 weeks, advantageously longer than 44 weeks, advantageously longer than 45 weeks, advantageously longer than 46 weeks, advantageously longer than 47 weeks, advantageously longer than 48 weeks, advantageously longer than 49 weeks, advantageously longer than 50 weeks, advantageously longer than 51 weeks, advantageously longer than 52 weeks, advantageously longer than 1 year, advantageously longer than 1.5 years, advantageously longer than 2 years, advantageously longer than 2.5 year, advantageously longer than 3 years, advantageously longer than 3.5 years, advantageously longer than 4 years.

In one aspect, the present disclosure provides a pharmaceutical composition comprising (i) a SGLT2 inhibitor as defined above and (ii) a PPAR agonist as defined above, as active ingredients. As used herein, the term "active ingredients" of a pharmaceutical composition according to the present disclosure means the SGLT2 inhibitor and/or PPAR agonist as defined herein.

In some embodiments, the present disclosure provides a pharmaceutical composition comprising (i) empagliflozin or a pharmaceutical acceptable salt thereof as defined herein and (ii) lanifibranor or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof as defined herein, as active ingredients. In some embodiment, a pharmaceutical composition or dosage form according to the present disclosure comprises lanifibranor, wherein at least 50 % by weight of lanifibranor is in the form of its crystalline form beta as defined herein. Preferably in said composition or dosage form at least 80 % by weight, advantageously at least 90 % by weight, advantageously at least 91 % by weight, advantageously at least 92 % by weight, advantageously at least 93 % by weight, advantageously at least 94 % by weight, advantageously at least 95 % by weight, advantageously at least 96 % by weight, advantageously at least 97 % by weight, advantageously at least 98 % by weight, advantageously at least 99 % by weight of lanifibranor is in the form of its crystalline form beta as defined herein.

In some embodiments, the pharmaceutical composition further comprises at least one pharmaceutically acceptable excipient.

In some embodiments, the pharmaceutical composition comprises (i) an SGLT2 inhibitor as defined above and (ii) a PPAR agonist as defined above, as active ingredient, and at least one pharmaceutically acceptable excipient.

In some embodiments, the pharmaceutical composition comprises (i) an SGLT2 inhibitor as defined above and (ii) a PPAR agonist as defined above, as active ingredient, and at least one pharmaceutically acceptable excipient, wherein the SGLT2 inhibitor is empagliflozin and wherein the PPAR agonist is lanifibranor.

In some embodiments, the pharmaceutical composition comprises (i) an SGLT2 inhibitor as defined above and (ii) a PPAR agonist as defined above, as active ingredient, and at least one pharmaceutically acceptable excipient, wherein the SGLT2 inhibitor is empagliflozin and the dosage of empagliflozin is from about 0.5 mg to about 1000 mg per day and wherein the PPAR agonist is lanifibranor and the dosage of lanifibranor is from about 4 mg to about 1200 mg per day.

In some embodiments, the SGLT2 inhibitor and the PPAR agonist can be formulated into a same and unique pharmaceutical composition or into two distinct and separate pharmaceutical compositions.

A pharmaceutical composition which is present as a separate or multiple dosage form, preferably as a kit of parts, is useful in combination therapy to flexibly suit the individual therapeutic needs of the patient.

In some embodiments, the pharmaceutical composition(s) may be formulated for oral, parenteral oral, parenteral (such as intramuscular, intravenous, intradermal or subcutaneous), rectal or topical routes of administration in liquid or solid form. Oral administration of the SGLT2 inhibitor is preferred. Oral administration of the PPAR agonist is preferred. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the active ingredient with one or more pharmaceutically acceptable carriers, like liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired formulation.

The pharmaceutical composition(s) may be formulated in the form of solutions, suspensions, emulsions, tablets, granules, fine granules, powders, capsules, caplets, soft capsules, pills, oral solutions, syrups, dry syrups, chewable tablets, troches, effervescent tablets, drops, fast dissolving tablets, oral fast-dispersing tablets. Advantageously, the pharmaceutical composition of the SGLT2 inhibitor is in the form of tablets. In some embodiments, the SGLT2 inhibitor is empagliflozin or a pharmaceutically acceptable salt thereof. Example of tablet formulations of empagliflozin are described in WO 2010/092126. Empagliflozin tablet formulations are marketed under the tradename Jardiance®. In some embodiments, the SGLT2 inhibitor is dapagliflozin or a pharmaceutically acceptable salt thereof. In some embodiments, the SGLT2 inhibitor is canagliflozin or a pharmaceutically acceptable

salt thereof. In some embodiments, the pharmaceutical composition of the PPAR agonist is in the form of tablets. In some embodiments, the PPAR agonist is lanifibranor, a deuterated form of lanifibranor or a pharmaceutically acceptable salt thereof. Examples of tablet formulations of lanifibranor are described in PCT/EP2024/051107.

In some embodiments, the pharmaceutical composition comprising (i) a SGLT2 inhibitor as defined herein and (ii) a PPAR agonist as defined herein, as active ingredients, is in the form of tablets. In some embodiments, the pharmaceutical composition of (i) empagliflozin or a pharmaceutical acceptable salt thereof as defined herein and (ii) lanifibranor or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof as defined herein is in the form of tablets. In some embodiments, the pharmaceutical composition of (i) empagliflozin and (ii) lanifibranor is in the form of tablets.

A pharmaceutical composition and dosage forms preferably comprise one or more pharmaceutical acceptable carriers. Preferred carriers must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Examples of pharmaceutically acceptable carriers are known to those skilled in the art.

A pharmaceutical composition may also be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredients may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution, for reconstitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use. Injectable formulations may be prepared according to known formulation techniques, e.g. using suitable liquid carriers, which usually comprise sterile water, and, optionally, further additives such as e.g. preservatives, pH adjusting agents, buffering agents, isotoning agents, solubility aids and/or tensides or the like, to obtain injectable solutions or suspensions. In addition, injectable formulations may comprise further additives, for example salts, solubility modifying agents or precipitating agents which retard release of the drug(s). Pharmaceutical compositions (or formulations) may be packaged in a variety of ways. Generally, an article for distribution includes one or more containers that contain the one or more pharmaceutical compositions in an appropriate form. Tablets are typically packed in an appropriate primary package for easy handling, distribution and storage

and for assurance of proper stability of the composition at prolonged contact with the environment during storage. Primary containers for tablets may be bottles or blister packs.

Solutions for injection may be available in typical suitable presentation forms such as vials, cartridges or prefilled (disposable) pens, which may be further packaged.

The article may further comprise a label or package insert, which refers to instructions customarily included in commercial packages of therapeutic products, that may contain information about the indications, usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products. In some embodiments, the label or package inserts indicates that the composition can be used for any of the purposes described hereinbefore or hereinafter.

Accordingly, in some embodiments, the SGLT2 inhibitor as defined herein can be used to prevent or delay clinical complications of the side effects resulting from the administration of the PPAR agonist in a patient, in particular blood disorders side effects, more particularly anaemia or clinical complications of anaemia. In some embodiments, in the context of the present invention, the SGLT2 inhibitor as defined herein can be used to prevent or delay clinical complications of the side effects in a patient who has been treated, is treated or is planned to be treated with a PPAR agonist. In some embodiments, the SGLT2 inhibitor as defined herein can be used to prevent or delay clinical complications of blood disorders resulting from the administration of the PPAR agonist in a patient. In some embodiments, the SGLT2 inhibitor as defined herein can be used to compensate the reduction of hemoglobin amount in a patient resulting from the administration of a PPAR agonist to the patient. In some embodiments, the SGLT2 inhibitor as defined herein can be used to compensate the reduction of hemoglobin amount in a patient who has been treated, is treated or is planned to be treated with a PPAR agonist.

In preferred embodiment, in the context of the present invention, the SGLT2 inhibitor as defined herein can be used to prevent or delay clinical anaemia or clinical complications of anaemia in a patient who has been treated, is treated or is planned to be treated with a PPAR agonist. In some embodiments, the SGLT2 inhibitor as defined herein can be used to prevent or delay anaemia or clinical complications of anaemia resulting from the administration of the PPAR agonist in a patient. In some embodiments, the SGLT2 inhibitor as defined herein can be used to compensate anaemia or clinical complications of anaemia in a patient resulting from the administration of a PPAR agonist to the patient. In some embodiments, the SGLT2 inhibitor as defined herein can be used to compensate anaemia in a patient who has been treated, is treated or is planned to be treated with a PPAR agonist.

In some embodiments, the SGLT2 inhibitor as defined herein can be used to prevent or delay clinical complications of the side effects resulting from the administration of lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof) as defined herein, in a patient, in particular blood disorders side effects, more particularly anaemia or clinical complications of anaemia. In some embodiments, the SGLT2 inhibitor as defined herein can be used to prevent or delay clinical complications of the side effects in a patient who has been treated, is treated or is planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof). In some embodiments, the SGLT2 inhibitor as defined herein can be used to prevent or delay clinical complications of blood disorders in a patient who has been treated, is treated or is planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof). In a preferred embodiment, the SGLT2 inhibitor as defined herein can be used to prevent or delay anaemia or clinical complications of anaemia in a patient who has been treated, is treated or is planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof). In some embodiments, the SGLT2 inhibitor as defined herein can be used to compensate the reduction of hemoglobin amount in a patient resulting from the administration of lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof) to the patient. In some embodiments, the SGLT2 inhibitor as defined herein can be used to compensate the reduction of hemoglobin amount in a patient who has been treated, is treated or is planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof). In some embodiments, the SGLT2 inhibitor as defined herein is used to compensate anaemia in a patient resulting from the administration of lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof) to the patient. In some embodiments, the SGLT2 inhibitor as defined herein can be used to compensate anaemia in a patient who has been treated, is treated or is planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof).

In some embodiments, empagliflozin or a pharmaceutical acceptable salt thereof can be used to prevent or delay clinical complications of the side effects resulting from the administration of lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof) as defined herein, in a patient, in particular blood disorders side effects, more particularly anaemia or clinical complications of anaemia. In some embodiments, empagliflozin or a pharmaceutical acceptable salt thereof can be used to prevent or delay clinical complications of the side effects in a patient who has been

treated, is treated or is planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof). In some embodiments, empagliflozin or a pharmaceutical acceptable salt thereof can be used to prevent or delay clinical complications of blood disorders in a patient who has been treated, is treated or is planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof). In a preferred embodiment, empagliflozin or a pharmaceutical acceptable salt thereof can be used to prevent or delay anaemia or clinical complications of anaemia in a patient who has been treated, is treated or is planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof). In some embodiments, empagliflozin or a pharmaceutical acceptable salt thereof can be used to compensate the reduction of hemoglobin amount in a patient resulting from the administration of lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof) to the patient. In some embodiments, empagliflozin or a pharmaceutical acceptable salt thereof can be used to compensate the reduction of hemoglobin amount in a patient who has been treated, is treated or is planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof). In some embodiments, empagliflozin or a pharmaceutical acceptable salt thereof can be used to compensate anaemia in a patient resulting from the administration of lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof) to the patient. In some embodiments, empagliflozin or a pharmaceutical acceptable salt thereof can be used to compensate anaemia in a patient who has been treated, is treated or is planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof).

In some embodiments, the SGLT2 inhibitor as defined herein can be used to compensate the weight gain in a patient resulting from the administration of a PPAR agonist to the patient. As described hereinbefore by the use or the administration of a pharmaceutical composition and in particular in view of the effect of the PPAR agonist therein, a reduction of body weight gain due to the administration of SGLT2 inhibitor may result, or no gain in body weight or even a reduction in body weight may result. In some embodiments, empagliflozin or a pharmaceutical acceptable salt thereof can be used to compensate the body weight gain in a patient resulting from the administration of lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof), in a patient.

In some embodiments, the SGLT2 inhibitor as defined herein can be used to reduce the amount of HbA1c in a patient suffering from liver disease and having been treated, treated or planned to be treated with a PPAR agonist. In some embodiments,

empagliflozin or a pharmaceutical acceptable salt thereof can be used to reduce the amount of HbA1c in a patient having been treated, treated or planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof).

In some embodiments, the SGLT2 inhibitor as defined herein can be used to improve liver parameters (alanine transaminase, aspartate transaminase, gamma glutamyl transferase) in a patient suffering from liver disease and having been treated, treated or planned to be treated with a PPAR agonist. In some embodiments, empagliflozin or a pharmaceutical acceptable salt thereof can be used to improve liver parameters in a patient having been treated, treated or planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof).

In some embodiments, the SGLT2 inhibitor as defined herein can be used to improve glycaemic control and insulin resistance in a patient suffering from liver disease and having been treated, treated or planned to be treated with a PPAR agonist. In some embodiments, empagliflozin or a pharmaceutical acceptable salt thereof can be used to improve glycaemic control and insulin resistance in a patient having been treated, treated or planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof).

In some embodiments, the SGLT2 inhibitor as defined herein can be used to improve lipids parameters (HDL-cholesterol, triglycerides) in a patient suffering from liver disease and having been treated, treated or planned to be treated with a PPAR agonist. In some embodiments, empagliflozin or a pharmaceutical acceptable salt thereof can be used to improve lipids parameters in a patient having been treated, treated or planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof).

In some embodiments, the SGLT2 inhibitor as defined herein can be used to reduce liver stiffness in a patient suffering from liver disease and having been treated, treated or planned to be treated with a PPAR agonist. In some embodiments, empagliflozin or a pharmaceutical acceptable salt thereof can be used to reduce liver stiffness in a patient having been treated, treated or planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof).

In some embodiments, the SGLT2 inhibitor as defined herein can be used to reduce liver fat in a patient suffering from liver disease and having been treated, treated or planned to be treated with a PPAR agonist. In some embodiments, empagliflozin or a pharmaceutical acceptable salt thereof can be used to reduce liver fat in a patient having been treated, treated or planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof).

In some embodiments, the SGLT2 inhibitor as defined herein can be used to reduce fibro-inflammation in a patient suffering from liver disease and having been treated, treated or planned to be treated with a PPAR agonist. In some embodiments, empagliflozin or a pharmaceutical acceptable salt thereof can be used to reduce fibro-inflammation in a patient having been treated, treated or planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof).

In some embodiments, the SGLT2 inhibitor as defined herein can be used to improve the ratio of visceral adipose tissue over subcutaneous adipose tissue in a patient suffering from liver disease and having been treated, treated or planned to be treated with a PPAR agonist. In some embodiments, empagliflozin or a pharmaceutical acceptable salt thereof can be used to improve the ratio of visceral adipose tissue over subcutaneous adipose tissue in a patient having been treated, treated or planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof).

In some embodiments, the SGLT2 inhibitor as defined herein can be used to improve the cardiometabolic health in a patient suffering from liver disease and having been treated, treated or planned to be treated with a PPAR agonist. In some embodiments, empagliflozin or a pharmaceutical acceptable salt thereof can be used to improve the cardiometabolic health in a patient having been treated, treated or planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof).

In one aspect of the present disclosure, SGLT2 inhibitors can be used to reduce or prevent the discontinuation of a treatment with a PPAR agonist in a patient treated with such PPAR agonist. In some embodiments, empagliflozin or a pharmaceutical acceptable salt thereof can be used to reduce or prevent the discontinuation of a treatment with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof) in a patient treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof).

In one aspect, the present disclosure provides a method for preventing or delaying clinical complications of blood disorders, preferably for preventing or delaying anaemia or clinical complications of anaemia, in a patient who has been treated, is treated or is planned to be treated with a PPAR agonist, said method comprising administering to said patient a suitable dosage of SGLT2 inhibitor. In some embodiments, the present disclosure provides a method for preventing or delaying clinical complications of blood disorders, preferably for preventing or delaying anaemia or clinical complications of

anaemia, in a patient who is already treated with a PPAR agonist, said method comprising administering to said patient a suitable dosage of SGLT2 inhibitor.

In some embodiments, the present disclosure provides a method for preventing or delaying clinical complications of blood disorders, preferably for preventing or delaying anaemia or clinical complications of anaemia, in a patient who has been treated, is treated or is planned to be treated with a PPAR agonist, said method comprising administering to said patient a suitable dosage of SGLT2 inhibitor, wherein said SGLT2 inhibitor and said PPAR agonist are administered in combination or alternation or sequentially to the patient. In some embodiments, the present disclosure provides a method for preventing or delaying clinical complications of blood disorders, preferably for preventing or delaying anaemia or clinical complications of anaemia, in a patient who is already treated with a PPAR agonist, said method comprising administering to said patient a suitable dosage of SGLT2 inhibitor, wherein said SGLT2 inhibitor and said PPAR agonist are administered in combination or alternation or sequentially to the patient.

In some embodiments, the present disclosure provides a method for preventing or delaying clinical complications of blood disorders, preferably for preventing or delaying anaemia or clinical complications of anaemia, in a patient who has been treated, is treated or is planned to be treated with a PPAR agonist, said method comprising administering to said patient a suitable dosage of SGLT2 inhibitor, wherein the first dose of SGLT2 inhibitor is administered at least one day after the start of the treatment with the PPAR agonist. In some embodiments, the present disclosure provides a method for preventing or delaying clinical complications of blood disorders, preferably for preventing or delaying anaemia or clinical complications of anaemia, in a patient who is already treated with a PPAR agonist, said method comprising administering to said patient a suitable dosage of SGLT2 inhibitor, wherein the first dose of SGLT2 inhibitor is administered at least one day after the start of the treatment with the PPAR agonist.

In some embodiments, the present disclosure provides a method for preventing or delaying clinical complications of blood disorders, preferably for preventing or delaying anaemia or clinical complications of anaemia, in a patient who has been treated, is treated or is planned to be treated with a PPAR agonist, said method comprising administering to said patient a suitable dosage of SGLT2 inhibitor, wherein the first dose of SGLT2 inhibitor is administered at the same time as the first dose of the treatment with the PPAR agonist. In some embodiments, the present disclosure provides a method for preventing or delaying clinical complications of blood disorders, preferably for preventing or delaying anaemia or clinical complications of anaemia, in

a patient who is already treated with a PPAR agonist, said method comprising administering to said patient a suitable dosage of SGLT2 inhibitor, wherein the first dose of SGLT2 inhibitor is administered at the same time as the first dose of the treatment with the PPAR agonist.

In some embodiments, the present disclosure provides a method for preventing or delaying clinical complications of blood disorders, preferably for preventing or delaying anaemia or clinical complications of anaemia, in a patient who has been treated, is treated or is planned to be treated with a PPAR agonist, said method comprising administering to said patient a suitable dosage of SGLT2 inhibitor, wherein the first dose of SGLT2 inhibitor is administered at least one day before the start of the treatment with the PPAR agonist. In some embodiments, the present disclosure provides a method for preventing or delaying clinical complications of blood disorders, preferably for preventing or delaying anaemia or clinical complications of anaemia, in a patient who is already treated with a PPAR agonist, said method comprising administering to said patient a suitable dosage of SGLT2 inhibitor, wherein the first dose of SGLT2 inhibitor is administered at least one day before the start of the treatment with the PPAR agonist.

In some embodiments, the suitable dosage of SGLT2 inhibitor is from about 0.5 mg to about 1000 mg for example from about 0.5 mg to about 500 mg, for example from about 0.5 mg to about 200 mg, for example from about 1 to about 100 mg, for example from about 1 to about 50 mg, for example from about 1 to about 25 mg per day. Particular dosage strengths (e.g. per tablet or capsule) are for example 1, 2.5, 5, 7.5, 10, 12.5, 15, 20, 25 or 50 mg of the SGLT2 inhibitor. In some embodiments, the SGLT2 inhibitor is administered once a day. In some embodiments, the SGLT2 inhibitor is administered once a day by oral route.

In some embodiments, the dosage of PPAR agonist is from about 4 mg to about 1200 mg per day. In some embodiments, the PPAR agonist is administered once a day. In some embodiments, the PPAR agonist is administered once a day by oral route. In some embodiments, the dosage of PPAR agonist is from about 400 mg to about 1200 mg per day.

In some embodiments, the present disclosure provides a method for preventing or delaying clinical complications of blood disorders, preferably for preventing or delaying anaemia or clinical complications of anaemia, in a patient who has been treated, is treated or is planned to be treated with a PPAR agonist, in particular in a patient who is already treated with a PPAR agonist, said method comprising administering to said patient a suitable dosage of SGLT2 inhibitor, wherein the SGLT2 inhibitor is selected from the group comprising canaglifozin, dapagliflozin, remoglifozin, sergliflozin,

empagliflozin, ipragliflozin, tofogliflozin, luseogliflozin, sotagliflozin, ertuglifozin, bexagliflozin, henagliflozin, janagliflozin, tianagliflozin, and pharmaceutically acceptable salts thereof.

In some embodiments, the present disclosure provides a method for preventing or delaying clinical complications of blood disorders, preferably for preventing or delaying anaemia or clinical complications of anaemia, in a patient who has been treated, is treated or is planned to be treated with a PPAR agonist, in particular in a patient who is already treated with a PPAR agonist, said method comprising administering to said patient a suitable dosage of SGLT2 inhibitor, wherein the PPAR agonist is selected from the group comprising lanifibranor, a deuterated form of lanifibranor and a pharmaceutically acceptable salt thereof.

In some embodiments, the present disclosure provides a method for preventing or delaying clinical complications of blood disorders, preferably for preventing or delaying anaemia or clinical complications of anaemia, in a patient who has been treated, is treated or is planned to be treated with a PPAR agonist, in particular in a patient who is already treated with a PPAR agonist, said method comprising administering to said patient a suitable dosage of SGLT2 inhibitor, wherein the patient is diagnosed with a liver disease. Advantageously, the liver disease is selected from liver fibrosis, liver steatosis, fatty liver disease, acute decompensation, 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), diabetes autoimmune cholangitis, primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), autoimmune cholangiopathy, hepatocarcinoma (HCC) and a combination of these diseases.

In some embodiments, the present disclosure provides a method for preventing or delaying clinical complications of blood disorders, preferably for preventing or delaying anaemia or clinical complications of anaemia, in a patient who has been treated, is treated or is planned to be treated with a PPAR agonist, in particular in a patient who is already treated with a PPAR agonist, said method comprising administering to said patient a suitable dosage of SGLT2 inhibitor, wherein blood disorders consist in a reduction in the amount of at least one biomarker compared to the reference amount of said at least one biomarker, wherein said at least one biomarker is selected from: hemoglobin, ferritin, haptoglobin, hematocrit, transferrin, vitamin B12 and a combination thereof. In some embodiments, the present disclosure provides a method for preventing or delaying anaemia or clinical complications of anaemia, in a patient who has been treated, is treated or is planned to be treated with a PPAR agonist, in

particular in a patient who is already treated with a PPAR agonist, said method comprising administering to said patient a suitable dosage of SGLT2 inhibitor, wherein anaemia consist in a reduction in the amount of at least one biomarker compared to the reference amount of said at least one biomarker, wherein said at least one biomarker is selected from: hemoglobin, ferritin, haptoglobin, hematocrit, transferrin, vitamin B12 and a combination thereof. Advantageously, the at least one biomarker is hemoglobin. Advantageously, the reduction in the amount of hemoglobin is equal to or greater than 5% to the reference amount of hemoglobin of said patient. Advantageously, the at least one biomarker is ferritin. In some embodiment, blood disorders are hemoglobin abnomalies. In some embodiments, the present disclosure provides a method for preventing or delaying clinical complications of blood disorders, in a patient who has been treated, is treated or is planned to be treated with a PPAR agonist, in particular in a patient who is already treated with a PPAR agonist, said method comprising administering to said patient a suitable dosage of SGLT2 inhibitor, wherein blood disorders are anaemia or clinical complications of anaemia.

In some embodiments, the present disclosure provides a method for preventing or delaying clinical complications of blood disorders, preferably for preventing or delaying anaemia or clinical complications of anaemia, in a patient who has been treated, is treated or is planned to be treated with a PPAR agonist, in particular in a patient who is already treated with a PPAR agonist, said method comprising administering to said patient a suitable dosage of SGLT2 inhibitor, wherein said patient:

1. is diagnosed with one or more of the conditions selected from the group consisting of overweight, obesity, visceral obesity and abdominal obesity; or
2. displays at least one of the following conditions:
    (a) being over the age of 40 years;
    (b) a poor iron absorption;
    (c) a body mass index equal to or greater than 30 kg/m2;
    (d) an HbA1c value equal to or greater than 7.0 %;
    (e) a amount of hemoglobin equal to or below 140 g/L;
    (f) diagnosed with one of the following diseases: diabetes, dyslipidemia, cardiovascular diseases, cancer, polycystic ovary syndrome, acute lung injury, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, insulin resistance, obesity, diseases linked to endothelial dysfunction, atherosclerosis, myocardial infarction, hypertension, cerebrovascular problems, inflammatory diseases such as rheumatoid arthritis, chronic kidney disease, a pulmonary fibrotic disorder such as idiopathic

pulmonary fibrosis, systemic sclerosis and neurodegeneration such as Alzheimer's disease or Parkinson's disease;

(g) diagnosed with a liver disease;

(h) diagnosed with non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), metabolic-associated fatty liver disease (MAFLD), and/or metabolic-associated steatohepatitis (MASH.

In some embodiments, the present disclosure provides a method for preventing or delaying clinical complications of blood disorders, preferably for preventing or delaying anaemia or clinical complications of anaemia, in a patient who has been treated, is treated or is planned to be treated with a PPAR agonist, in particular in patient who is already treated with a PPAR agonist, said method comprising administering to said patient a suitable dosage of SGLT2 inhibitor, wherein said patient further displays at least one of the following conditions:

a. aspartate aminotransferase (AST) amount greater than or equal to 10.0 U/L;
b. alanine aminotransferase (ALT) amount greater than or equal to 10.0 U/L;
c. gamma glutamyl transferase (GGT) amount greater than or equal to 3.0 U/L;
d. fasting blood glucose amount greater than or equal to 4.0 mmol/L;
e. HDL-cholesterol blood amount below than or equal to 2.50 mmol/L;
f. triglyceride blood amount greater than or equal to 0.70 mmol/L;
g. ferritin amount greater than or equal to 6.0 µg/L;
h. a systolic blood pressure greater than or equal to 95 mm Hg and a diastolic blood pressure greater than or equal to 60 mm Hg;
i. ratio visceral adipose tissue (VAT)/ subcutaneous adipose tissue (SAT) (VAT/SAT) greater than or equal to 0.30;
j. cT1 amount greater than or equal to 700 ms.

In one aspect, the present disclosure provides a method for preventing or delaying clinical complications of a reduction in the amount of hemoglobin, in a patient who has been treated, is treated or is planned to be treated with a PPAR agonist, in particular in a patient who is already treated with a PPAR agonist, said method comprising administering to said patient a suitable dose of SGLT2 inhibitor.

In one aspect, the present disclosure provides a method for preventing or delaying anaemia or clinical complications of anaemia, in a patient who has been treated, is treated or is planned to be treated with a PPAR agonist, in particular in a patient who is already treated with a PPAR agonist, said method comprising administering to said patient a suitable dose of SGLT2 inhibitor.

In one aspect, the present disclosure provides a method for preventing or delaying clinical complications of blood disorders, preferably for preventing or delaying anaemia

or clinical complications of anaemia, in a patient diagnosed with a liver disease, said method comprising administering to said patient a SGLT2 inhibitor and a PPAR agonist.

In one aspect, the present disclosure provides a method for preventing or delaying clinical complications of blood disorders, preferably for preventing or delaying anaemia or clinical complications of anaemia, in a patient who has been treated, is treated or is planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof), said method comprising administering to said patient a suitable dosage of empagliflozin (or a pharmaceutical acceptable salt thereof). In some embodiments, the present disclosure provides a method for preventing or delaying clinical complications of blood disorders, preferably for preventing or delaying anaemia or clinical complications of anaemia, in a patient who is already treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof), said method comprising administering to said patient a suitable dosage of empagliflozin (or a pharmaceutical acceptable salt thereof).

In some embodiments, the present disclosure provides a method for preventing or delaying clinical complications of blood disorders, preferably for preventing or delaying anaemia or clinical complications of anaemia, in a patient who has been treated, is treated or is planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof), said method comprising administering to said patient a suitable dosage of empagliflozin (or a pharmaceutical acceptable salt thereof), wherein said empagliflozin (or a pharmaceutical acceptable salt thereof) and lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof) are administered in combination or alternation or sequentially to the patient. In some embodiments, the present disclosure provides a method for preventing or delaying clinical complications of blood disorders, preferably for preventing or delaying anaemia or clinical complications of anaemia, in a patient who is already treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof), said method comprising administering to said patient a suitable dosage of empagliflozin (or a pharmaceutical acceptable salt thereof), wherein empagliflozin (or a pharmaceutical acceptable salt thereof) and lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof) are administered in combination or alternation or sequentially to the patient.

In some embodiments, the present disclosure provides a method for preventing or delaying clinical complications of blood disorders, preferably for preventing or delaying anaemia or clinical complications of anaemia, in a patient who has been treated, is

treated or is planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof), said method comprising administering to said patient a suitable dosage of empagliflozin (or a pharmaceutical acceptable salt thereof), wherein the first dose of empagliflozin (or a pharmaceutical acceptable salt thereof) is administered at least one day after the start of the treatment with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof). In some embodiments, the present disclosure provides a method for preventing or delaying clinical complications of blood disorders, preferably for preventing or delaying anaemia or clinical complications of anaemia, in a patient who is already treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof), said method comprising administering to said patient a suitable dosage of empagliflozin (or a pharmaceutical acceptable salt thereof), wherein the first dose of empagliflozin (or a pharmaceutical acceptable salt thereof) is administered at least one day after the start of the treatment with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof).

In some embodiments, the present disclosure provides a method for preventing or delaying clinical complications of blood disorders, preferably for preventing or delaying anaemia or clinical complications of anaemia, in a patient who has been treated, is treated or is planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof), said method comprising administering to said patient a suitable dosage of empagliflozin (or a pharmaceutical acceptable salt thereof), wherein the first dose of empagliflozin (or a pharmaceutical acceptable salt thereof) is administered at the same time as the first dose of the treatment with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof). In some embodiments, the present disclosure provides a method for preventing or delaying clinical complications of blood disorders, preferably for preventing or delaying anaemia or clinical complications of anaemia, in a patient who is already treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof), said method comprising administering to said patient a suitable dosage of empagliflozin (or a pharmaceutical acceptable salt thereof), wherein the first dose of empagliflozin (or a pharmaceutical acceptable salt thereof) is administered at the same time as the first dose of the treatment with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof).

In some embodiments, the present disclosure provides a method for preventing or delaying clinical complications of blood disorders, preferably for preventing or delaying

anaemia or clinical complications of anaemia, in a patient who has been treated, is treated or is planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof), said method comprising administering to said patient a suitable dosage of empagliflozin (or a pharmaceutical acceptable salt thereof), wherein the first dose of empagliflozin (or a pharmaceutical acceptable salt thereof) is administered at least one day before the start of the treatment with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof). In some embodiments, the present disclosure provides a method for preventing or delaying clinical complications of blood disorders, preferably for preventing or delaying anaemia or clinical complications of anaemia, in a patient who is already treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof), said method comprising administering to said patient a suitable dosage of empagliflozin (or a pharmaceutical acceptable salt thereof), wherein the first dose of empagliflozin (or a pharmaceutical acceptable salt thereof) is administered at least one day before the start of the treatment with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof).

In some embodiments, the suitable dosage of empagliflozin (or a pharmaceutical acceptable salt thereof) is from about 0.5 mg to about 1000 mg for example from about 0.5 mg to about 500 mg, for example from about 0.5 mg to about 200 mg, for example from about 1 to about 100 mg, for example from about 1 to about 50 mg, for example from about 1 to about 25 mg per day. Particular dosage strengths (e.g. per tablet or capsule) are for example 1, 2.5, 5, 7.5, 10, 12.5, 15, 20, 25 or 50 mg of empagliflozin (or a pharmaceutical acceptable salt thereof). In some embodiments, empagliflozin (or a pharmaceutical acceptable salt thereof) is administered once a day. In some embodiments, empagliflozin (or a pharmaceutical acceptable salt thereof) is administered once a day by oral route.

In some embodiments, the dosage of lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof) is from about 400 mg to about 1200 mg per day. In some embodiments, lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof) is administered once a day. In some embodiments, lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof) is administered once a day by oral route.

In some embodiments, the present disclosure provides a method for preventing or delaying clinical complications of blood disorders, preferably for preventing or delaying anaemia or clinical complications of anaemia, in a patient who has been treated, is treated or is planned to be treated with lanifibranor (or a deuterated form of

lanifibranor or a pharmaceutical acceptable salt thereof), in particular in a patient who is already treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof), said method comprising administering to said patient a suitable dosage of empagliflozin (or a pharmaceutical acceptable salt thereof), wherein the patient is diagnosed with a liver disease. In some embodiments, the liver disease is selected from liver fibrosis, liver steatosis, fatty liver disease, acute decompensation, 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), diabetes, autoimmune cholangitis, primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), autoimmune cholangiopathy, hepatocarcinoma (HCC) and a combination of these diseases.

In some embodiments, the present disclosure provides a method for preventing or delaying clinical complications of blood disorders, in a patient who has been treated, is treated or is planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof), in particular in a patient who is already treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof), said method comprising administering to said patient a suitable dosage of empagliflozin (or a pharmaceutical acceptable salt thereof), wherein blood disorders consist in a reduction in the amount of at least one biomarker compared to the reference amount of said at least one biomarker, wherein said at least one biomarker is selected from: hemoglobin, ferritin, haptoglobin, hematocrit, transferrin, vitamin B12 and a combination thereof. In some embodiments, the present disclosure provides a method for preventing or delaying anaemia or clinical complications of anaemia , in a patient who has been treated, is treated or is planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof), in particular in a patient who is already treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof), said method comprising administering to said patient a suitable dosage of empagliflozin (or a pharmaceutical acceptable salt thereof), wherein anaemia consist in a reduction in the amount of at least one biomarker compared to the reference amount of said at least one biomarker, wherein said at least one biomarker is selected from: hemoglobin, ferritin, haptoglobin, hematocrit, transferrin, vitamin B12 and a combination thereof. Advantageously, the at least one biomarker is hemoglobin. Advantageously, the reduction in the amount of hemoglobin is equal to or greater than 5% to the reference amount of hemoglobin of

said patient. Advantageously, the at least one biomarker is ferritin. In some embodiment, blood disorders are hemoglobin abnomalies. In some embodiments, the reduction in the amount of hemoglobin is equal to or greater than 5% to the reference amount of hemoglobin of said patient.

In some embodiments, the present disclosure provides a method for preventing or delaying clinical complications of blood disorders, preferably for preventing or delaying anaemia or clinical complications of anaemia, in a patient who has been treated, is treated or is planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof), in particular in a patient who is already treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof), said method comprising administering to said patient a suitable dosage of empagliflozin (or a pharmaceutical acceptable salt thereof), wherein said patient:

1. is diagnosed with one or more of the conditions selected from the group consisting of overweight, obesity, visceral obesity and abdominal obesity; or
2. displays at least one of the following conditions before treatment with a PPAR agonist:
    (a) being over the age of 40 years;
    (b) a poor iron absorption;
    (c) a body mass index equal to or greater than 30 kg/m^2;
    (d) a reference amount of HbA1c equal to or greater than 7.0 %;
    (e) a reference amount of hemoglobin equal to or below 140 g/L;
    (f) diagnosed with one of the following diseases: diabetes, dyslipidemia, cardiovascular diseases, cancer, polycystic ovary syndrome, acute lung injury, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, insulin resistance, obesity, diseases linked to endothelial dysfunction, atherosclerosis, myocardial infarction, hypertension, cerebrovascular problems, inflammatory diseases such as rheumatoid arthritis, chronic kidney disease, a pulmonary fibrotic disorder such as idiopathic pulmonary fibrosis, systemic sclerosis and neurodegeneration such as Alzheimer's disease or Parkinson's disease;
    (g) diagnosed with a liver disease;
    (h) diagnosed with non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), metabolic-associated fatty liver disease (MAFLD), and/or metabolic-associated steatohepatitis (MASH.

In some embodiments, the present disclosure provides a method for preventing or delaying clinical complications of blood disorders, preferably for preventing or delaying

anaemia or clinical complications of anaemia, in a patient who has been treated, is treated or is planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof), in particular in a patient who is already treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof), said method comprising administering to said patient a suitable dosage of empagliflozin (or a pharmaceutical acceptable salt thereof), wherein said patient further displays at least one of the following conditions before treatment with a PPAR agonist:

a. aspartate aminotransferase (AST) amount greater than or equal to 10.0 U/L;
b. alanine aminotransferase (ALT) amount greater than or equal to 10.0 U/L;
c. gamma glutamyl transferase (GGT) amount greater than or equal to 3.0 U/L;
d. fasting blood glucose amount greater than or equal to 4.0 mmol/L;
e. HDL-cholesterol blood amount below than or equal to 2.50 mmol/L;
f. triglyceride blood amount greater than or equal to 0.70 mmol/L;
g. ferritin amount greater than or equal to 6.0 µg/L;
h. a systolic blood pressure greater than or equal to 95 mm Hg and a diastolic blood pressure greater than or equal to 60 mm Hg;
i. ratio visceral adipose tissue (VAT)/ subcutaneous adipose tissue (SAT) (VAT/SAT) greater than or equal to 0.30;
j. cT1 amount greater than or equal to 700 ms.

In one aspect, the present disclosure provides a method for preventing or delaying clinical complications of a reduction in the amount of hemoglobin, in a patient who has been treated, is treated or is planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof), in particular in a patient who is already treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof), said method comprising administering to said patient a suitable dosage of empagliflozin (or a pharmaceutical acceptable salt thereof).

In one aspect, the present disclosure provides a method for preventing or delaying anaemia or clinical complications of anaemia, in a patient who has been treated, is treated or is planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof), in particular in a patient who is already treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof), said method comprising administering to said patient a suitable dosage of empagliflozin (or a pharmaceutical acceptable salt thereof).

In one aspect, the present disclosure provides a method for preventing or delaying clinical complications of blood disorders, in a patient diagnosed with a liver disease, said method comprising administering to said patient lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof) and empagliflozin (or a pharmaceutical acceptable salt thereof).

In one aspect, the present disclosure provides a method for preventing or delaying anaemia or clinical complications of anaemia, in a patient diagnosed with a liver disease, said method comprising administering to said patient lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof) and empagliflozin (or a pharmaceutical acceptable salt thereof).

In one aspect, the present disclosure provides a method for preventing a reduction in the amount of hemoglobin in a patient who has been treated, is treated or is planned to be treated with a PPAR agonist, comprising administering to said patient a suitable dosage of SGLT2 inhibitor. In some embodiments, the SGLT2 inhibitor is empagliflozin or a pharmaceutical acceptable salt thereof, and the PPAR agonist is lanifibranor or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof.

In one aspect, the present disclosure provides a method for preventing a reduction in the amount of hemoglobin in a patient resulting from the administration of lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof) to the patient.

In one aspect, the present disclosure provides a method for preventing anaemia or clinical complications of anaemia, in a patient, resulting from the administration of a PPAR agonist, in particular lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof) to the patient, said method comprising administering to the patient a suitable dosage of SGLT2 inhibitor, in particular empagliflozin or a pharmaceutically acceptable salt thereof.

In one aspect, the present disclosure provides a method for preventing anaemia or clinical complications of anaemia, in a patient who has been treated, is treated or is planned to be treated with a PPAR agonist, in particular lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof), said method comprising administering to the patient a suitable dosage of SGLT2 inhibitor, in particular empagliflozin or a pharmaceutically acceptable salt thereof.

In one aspect, the present disclosure provides a method for reducing body weight or body fat, or for preventing an increase of body weight or for attenuating an increase of body weight in a patient treated for a liver disease, said method comprising administering to said patient a SGLT2 inhibitor and a PPAR agonist.

In one aspect, the present disclosure provides a method for reducing body weight or body fat, or for preventing an increase of body weight or for attenuating an increase of body weight in a patient treated for a liver disease, said method comprising administering to said patient a SGLT2 inhibitor and a PPAR agonist, wherein said SGLT2 inhibitor and said PPAR agonist are administered in combination or alternation or sequentially to the patient.

As disclosed herein, the SGLT2 inhibitor can be used to compensate body weight gain in a patient resulting from the administration of a PPAR agonist to the patient. As described hereinbefore by the use or the administration of a pharmaceutical composition and in particular in view of the effect of the PPAR agonist therein, a reduction of body weight gain due to the administration of the SGLT2 inhibitor may result, or no gain in body weight or even a reduction in body weight may result. In some embodiments, empagliflozin or a pharmaceutical acceptable salt thereof can be used to compensate the body weight gain in a patient resulting from the administration of lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof), to a patient.

In one aspect, the present disclosure provides a method for reducing the amount of HbA1c in a patient treated for a liver disease, said method comprising administering to said patient a SGLT2 inhibitor and a PPAR agonist. In one aspect, the present disclosure provides a method for reducing the amount of HbA1c in a patient treated for a liver disease, said method comprising administering to said patient a SGLT2 inhibitor and a PPAR agonist, wherein said SGLT2 inhibitor and said PPAR agonist are administered in combination or alternation or sequentially to the patient. As disclosed herein, the SGLT2 inhibitor can be used to reduce the amount of HbA1c in a patient having been treated, treated or planned to be treated with a PPAR agonist. In some embodiments, empagliflozin or a pharmaceutical acceptable salt thereof can be used to reduce the amount of HbA1c in a patient having been treated, treated or planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof).

In one aspect, the present disclosure provides a method for improving liver parameters (alanine transaminase, aspartate transaminase, gamma glutamyl transferase) in a patient treated for a liver disease, said method comprising administering to said patient a SGLT2 inhibitor and a PPAR agonist. In one aspect, the present disclosure provides a method for improving liver parameters in a patient treated for a liver disease, said method comprising administering to said patient a SGLT2 inhibitor and a PPAR agonist, wherein said SGLT2 inhibitor and said PPAR agonist are administered in combination or alternation or sequentially to the patient.

As disclosed herein, the SGLT2 inhibitor can be used to improve liver parameters in a patient having been treated, treated or planned to be treated with a PPAR agonist. In some embodiments, empagliflozin or a pharmaceutical acceptable salt thereof can be used to improve liver parameters in a patient having been treated, treated or planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof).

In one aspect, the present disclosure provides a method for improving glycaemic control and insulin resistance in a patient treated for a liver disease, said method comprising administering to said patient a SGLT2 inhibitor and a PPAR agonist. In one aspect, the present disclosure provides a method for improving glycaemic control and insulin resistance in a patient treated for a liver disease, said method comprising administering to said patient a SGLT2 inhibitor and a PPAR agonist, wherein said SGLT2 inhibitor and said PPAR agonist are administered in combination or alternation or sequentially to the patient. As disclosed herein, the SGLT2 inhibitor can be used to improve glycaemic control and insulin resistance in a patient having been treated, treated or planned to be treated with a PPAR agonist. In some embodiments, empagliflozin or a pharmaceutical acceptable salt thereof can be used to improve glycaemic control and insulin resistance in a patient having been treated, treated or planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof).

In one aspect, the present disclosure provides a method for improving lipids parameters (HDL-cholesterol, triglycerides) in a patient treated for a liver disease, said method comprising administering to said patient a SGLT2 inhibitor and a PPAR agonist. In one aspect, the present disclosure provides a method for improving lipids parameters in a patient treated for a liver disease, said method comprising administering to said patient a SGLT2 inhibitor and a PPAR agonist, wherein said SGLT2 inhibitor and said PPAR agonist are administered in combination or alternation or sequentially to the patient. As disclosed herein, the SGLT2 inhibitor can be used to improve lipids parameters in a patient having been treated, treated or planned to be treated with a PPAR agonist. In some embodiments, empagliflozin or a pharmaceutical acceptable salt thereof can be used to improve lipids parameters in a patient having been treated, treated or planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof).

In one aspect, the present disclosure provides a method for reducing liver stiffness in a patient treated for a liver disease, said method comprising administering to said patient a SGLT2 inhibitor and a PPAR agonist. In one aspect, the present disclosure provides a method for reducing liver stiffness in a patient treated for a liver disease,

said method comprising administering to said patient a SGLT2 inhibitor and a PPAR agonist, wherein said SGLT2 inhibitor and said PPAR agonist are administered in combination or alternation or sequentially to the patient. As disclosed herein, the SGLT2 inhibitor can be used to reduce liver stiffness in a patient having been treated, treated or planned to be treated with a PPAR agonist. In some embodiments, empagliflozin or a pharmaceutical acceptable salt thereof can be used to reduce liver stiffness in a patient having been treated, treated or planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof).

In one aspect, the present disclosure provides a method for reducing liver fat in a patient treated for a liver disease, said method comprising administering to said patient a SGLT2 inhibitor and a PPAR agonist. In one aspect, the present disclosure provides a method for reducing liver fat in a patient treated for a liver disease, said method comprising administering to said patient a SGLT2 inhibitor and a PPAR agonist, wherein said SGLT2 inhibitor and said PPAR agonist are administered in combination or alternation or sequentially to the patient. As disclosed herein, the SGLT2 inhibitor can be used to reduce liver fat in a patient having been treated, treated or planned to be treated with a PPAR agonist. In some embodiments, empagliflozin or a pharmaceutical acceptable salt thereof can be used to reduce liver fat in a patient having been treated, treated or planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof).

In one aspect, the present disclosure provides a method for reducing fibro-inflammation in a patient treated for a liver disease, said method comprising administering to said patient a SGLT2 inhibitor and a PPAR agonist. In one aspect, the present disclosure provides a method for reducing fibro-inflammation in a patient treated for a liver disease, said method comprising administering to said patient a SGLT2 inhibitor and a PPAR agonist, wherein said SGLT2 inhibitor and said PPAR agonist are administered in combination or alternation or sequentially to the patient. As disclosed herein, the SGLT2 inhibitor can be used to reduce fibro-inflammation in a patient having been treated, treated or planned to be treated with a PPAR agonist. In some embodiments, empagliflozin or a pharmaceutical acceptable salt thereof can be used to reduce fibro-inflammation in a patient having been treated, treated or planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof).

In one aspect, the present disclosure provides a method for improving the ratio of visceral adipose tissue over subcutaneous adipose tissue in a patient treated for a liver disease, said method comprising administering to said patient a SGLT2 inhibitor and a

PPAR agonist. In one aspect, the present disclosure provides a method for for improving the ratio of visceral adipose tissue over subcutaneous adipose tissue in a patient treated for a liver disease, said method comprising administering to said patient a SGLT2 inhibitor and a PPAR agonist, wherein said SGLT2 inhibitor and said PPAR agonist are administered in combination or alternation or sequentially to the patient. As disclosed herein, the SGLT2 inhibitor can be used to improve the ratio of visceral adipose tissue over subcutaneous adipose tissue in a patient having been treated, treated or planned to be treated with a PPAR agonist. In some embodiments, empagliflozin or a pharmaceutical acceptable salt thereof can be used to improve the ratio of visceral adipose tissue over subcutaneous adipose tissue in a patient having been treated, treated or planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof). As disclosed herein, the SGLT2 inhibitor can be used to improve the cardiometabolic health in a patient having been treated, treated or planned to be treated with a PPAR agonist. In some embodiments, empagliflozin or a pharmaceutical acceptable salt thereof can be used to improve the cardiometabolic health in a patient having been treated, treated or planned to be treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof).

In one aspect, the present disclosure provides a method for reducing or preventing the discontinuation of a treatment with a PPAR agonist in a patient treated with such PPAR agonist, said method comprising administering to said patient a SGLT2 inhibitor. In some embodiments, empagliflozin or a pharmaceutical acceptable salt thereof can be used to reduce or prevent the discontinuation of a treatment with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof) in a patient treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof).

In one aspect, the present disclosure provides a method for reducing or preventing the discontinuation of a treatment with lanifibranor or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof) in a patient treated with lanifibranor (or a deuterated form of lanifibranor or a pharmaceutical acceptable salt thereof), said method comprising administering empagliflozin (or a pharmaceutical acceptable salt thereof) to said patient.

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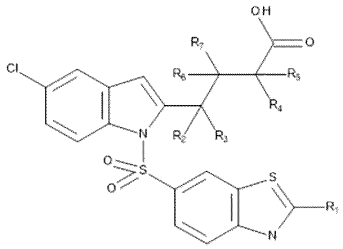
Aspects of the present disclosure are further illustrated by reference to the following, non-limiting items.

1. Sodium glucose transporter 2 (SGLT2) inhibitor for use for preventing or delaying clinical complications of blood disorders in a patient having been treated, treated or planned to be treated with a PPAR agonist.

2. The SGLT2 inhibitor for use according to item 1, wherein the SGLT2 inhibitor is selected from the group comprising canaglifozin, dapagliflozin, remoglifozin, sergliflozin, empagliflozin, ipragliflozin, tofogliflozin, luseogliflozin, sotagliflozin, ertuglifozin, bexagliflozin, henagliflozin, janagliflozin, tianagliflozin, and pharmaceutically acceptable salts thereof, preferably the SGLT2 inhibitor is empagliflozin.

3. The SGLT2 inhibitor for use according to any one of items 1 to 2, wherein the PPAR agonist is selected from the group comprising lanifibranor, a deuterated form of lanifibranor and pharmaceutically acceptable salts thereof.

4. The SGLT2 inhibitor for use according to item 3, 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, preferably 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.

5. The SGLT2 inhibitor for use according to any one of items 1 to 4, wherein the patient is diagnosed with a liver disease.

6. The SGLT2 inhibitor for use according to item 5, wherein the liver disease is selected from liver fibrosis, liver steatosis, fatty liver disease, acute decompensation, 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), diabetes, autoimmune cholangitis, primary biliary cholangitis, primary sclerosing cholangitis, autoimmune cholangiopathy, hepatocarcinoma and a combination of these diseases.

7. The SGLT2 inhibitor for use according to any one of items 1 to 6, wherein blood disorders consist in a reduction in the amount of at least one biomarker compared to

the reference amount of said at least one biomarker, wherein said at least one biomarker is selected from: hemoglobin, ferritin, haptoglobin, hematocrit, transferrin, vitamin B12 and a combination thereof.

8. The SGLT2 inhibitor for use according to item 7, wherein the reduction in the amount of at least one biomarker is equal or greater than 5% compared to the reference amount of at least one biomarker of said patient.

9. The SGLT2 inhibitor for use according to any one of items 1 to 8, wherein said patient:

a. is diagnosed with one or more conditions selected from the group consisting of overweight, obesity, visceral obesity and abdominal obesity; or
b. displays at least one of the following conditions:
    a. being over the age of 40 years;
    b. a poor iron absorption;
    c. a body mass index equal to or greater than 30 kg/m^2;
    d. a reference amount of HbA1c equal to or greater than 7.0 %;
    e. a reference amount of hemoglobin equal or below than 140 g/L;
    f. diagnosed with one of the following diseases: diabetes, dyslipidemia, cardiovascular diseases, cancer, polycystic ovary syndrome, acute lung injury, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, insulin resistance, obesity, diseases linked to endothelial dysfunction, atherosclerosis, myocardial infarction, hypertension, cerebrovascular problems, inflammatory diseases such as rheumatoid arthritis, chronic kidney disease, a pulmonary fibrotic disorder such as idiopathic pulmonary fibrosis, systemic sclerosis and neurodegeneration such as Alzheimer's disease or Parkinson's disease;
    g. diagnosed with a liver disease;
    h. diagnosed with non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), metabolic-associated fatty liver disease (MAFLD), metabolic-associated steatohepatitis (MASH) and/or diabetes.

10. The SGLT2 inhibitor for use according to any one of items 1 to 9, wherein said patient further displays at least one of the following conditions:

a. aspartate aminotransferase (AST) amount greater than or equal to 10.0 U/L;
b. alanine aminotransferase (ALT) amount greater than or equal to 10.0 U/L;
c. gamma glutamyl transferase (GGT) amount greater than or equal to 3.0 U/L;
d. fasting blood glucose amount greater than or equal to 4.0 mmol/L;
e. HDL-cholesterol blood amount below than or equal to 2.50 mmol/L;
f. triglyceride blood amount greater than or equal to 0.70 mmol/L;

g. ferritin amount greater than or equal to 6.0 µg/L;

h. a systolic blood pressure greater than or equal to 95 mm Hg and a diastolic blood pressure greater than or equal to 60 mm Hg;

i. ratio visceral adipose tissue (VAT)/ subcutaneous adipose tissue (SAT) (VAT/SAT) greater than or equal to 0.30;

j. cT1 amount greater than or equal to 700 ms.

11. The SGLT2 inhibitor for use according to any one of items 1 to 10, wherein said prevention comprises the administration in combination or alternation or sequentially of the PPAR agonist and the SGLT2 inhibitor.

12. The SGLT2 inhibitor for use according to any one of items 1 to 11, wherein the patient is treated or is planned to be treated with a PPAR agonist and the first dose of SGLT2 inhibitor is:

a. administered at least one day after the start of the treatment with the PPAR agonist; or

b. administered at the same time as the first dose of the treatment with the PPAR agonist; or

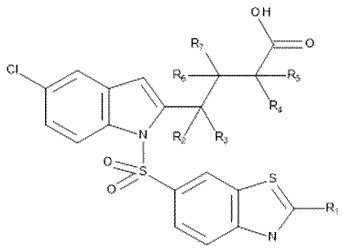
c. administered at least one day before the start of the treatment with the PPAR agonist.

13. A method for preventing or delaying clinical complications of blood disorders, in patient having been treated, treated or being planned to be treated with a PPAR agonist, said method comprising administering to said patient a suitable dosage of a SGLT2 inhibitor.

14. The method according to item 13, wherein the SGLT2 inhibitor is selected from the group comprising canaglifozin, dapagliflozin, remoglifozin, sergliflozin, empagliflozin, ipragliflozin, tofogliflozin, luseogliflozin, sotagliflozin, ertuglifozin, bexagliflozin, henagliflozin, janagliflozin, tianagliflozin, and a pharmaceutically acceptable salt thereof, preferably the SGLT2 inhibitor is empagliflozin.

15. The method according to any one of items 13 to 14, wherein the PPAR agonist is selected from the group comprising lanifibranor, a deuterated form of lanifibranor and pharmaceutically acceptable salts thereof.

16. The method according to item 15, 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, preferably 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.

17. The method according to any one of items 13 to 16, wherein the patient is diagnosed with a liver disease.

18. The method according to item 17, wherein the liver disease is selected from liver fibrosis, liver steatosis, fatty liver disease, acute decompensation, 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), diabetes, autoimmune cholangitis, primary biliary cholangitis, primary sclerosing cholangitis, autoimmune cholangiopathy, hepatocarcinoma and a combination of these diseases.

19. The method according to any one of items 13 to 18, wherein blood disorders consist in a reduction in the amount of at least one biomarker compared to the reference amount of said at least one biomarker, wherein said at least one biomarker is selected from: hemoglobin, ferritin, haptoglobin, unsaturated iron binding capacity, iron, lactate dehydrogenase, hematocrit, transferrin, vitamin B12, vitamin B9 and a combination thereof.

20. The method according to item 19, wherein the reduction in the amount of at least one biomarker is equal or greater than 5% compared to the reference amount of at least one biomarker of said patient.

21. The method according to any one of items 13 to 20, wherein said patient:

a. is diagnosed with one or more of the conditions selected from the group consisting of overweight, obesity, visceral obesity and abdominal obesity; or
b. displays at least one of the following conditions:
    a. being over the age of 40 years;
    b. a poor iron absorption;
    c. a body mass index equal to or greater than 30 kg/m2;

d. a reference amount of HbA1c equal to or greater than 7.0 %;
e. a reference amount of hemoglobin equal to or below than 140 g/L;
f. diagnosed with one of the following diseases: diabetes, dyslipidemia, cardiovascular diseases, cancer, polycystic ovary syndrome, acute lung injury, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, insulin resistance, obesity, diseases linked to endothelial dysfunction, atherosclerosis, myocardial infarction, hypertension, cerebrovascular problems, inflammatory diseases such as rheumatoid arthritis, chronic kidney disease, a pulmonary fibrotic disorder such as idiopathic pulmonary fibrosis, systemic sclerosis and neurodegeneration such as Alzheimer's disease or Parkinson's disease;
g. diagnosed with a liver disease;;
h. diagnosed with non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), metabolic-associated fatty liver disease (MAFLD), metabolic-associated steatohepatitis (MASH) and/or diabetes.

22. The method according to any one of items 13 to 21, wherein said patient further displays at least one of the following conditions:

a. aspartate aminotransferase (AST) amount greater than or equal to 10.0 U/L;
b. alanine aminotransferase (ALT) amount greater than or equal to 10.0 U/L;
c. gamma glutamyl transferase (GGT) amount greater than or equal to 3.0 U/L;
d. fasting blood glucose amount greater than or equal to 4.0 mmol/L;
e. HDL-cholesterol blood amount below than or equal to 2.50 mmol/L;
f. triglyceride blood amount greater than or equal to 0.70 mmol/L;
g. ferritin amount greater than or equal to 6.0 µg/L;
h. a systolic blood pressure greater than or equal to 95 mm Hg and a diastolic blood pressure greater than or equal to 60 mm Hg;
i. ratio visceral adipose tissue (VAT)/ subcutaneous adipose tissue (SAT) (VAT/SAT) greater than or equal to 0.30;
j. cT1 amount greater than or equal to 700 ms.

23. The method according to any one of items 13 to 22, wherein said prevention comprises the administration in combination or alternation or sequentially of the PPAR agonist and the SGLT2 inhibitor.

24. The method according to any one of items 13 to 23, wherein the patient is treated or is planned to be treated with a PPAR agonist and wherein the first dose of SGLT2 inhibitor is:

a. administered at least one day after the start of the treatment with the PPAR agonist; or

b. administered at the same time as the first dose of the treatment with the PPAR agonist; or

c. administered at least one day before the start of the treatment with the PPAR agonist.

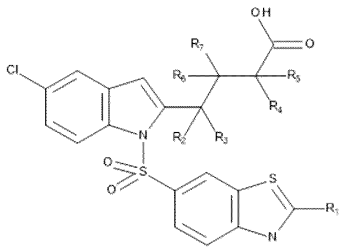
25. The method according to any one of items 13 to 24, wherein said PPAR agonist is lanifibranor a deuterated form of lanifibranor or a pharmaceutically acceptable salt thereof and said SGLT2 inhibitor is empagliflozin or a pharmaceutically acceptable salt thereof.

26. A method for preventing a reduction in the amount of hemoglobin in a patient having been treated, treated or planned to be treated with a PPAR agonist, comprising administering to the patient a suitable dosage of SGLT2 inhibitor.

27. The method according to item 26, wherein the SGLT2 inhibitor is selected from the group comprising canaglifozin, dapagliflozin, remoglifozin, sergliflozin, empagliflozin, ipragliflozin, tofogliflozin, luseogliflozin, sotagliflozin, ertuglifozin, bexagliflozin, henagliflozin, janagliflozin, tianagliflozin, and pharmaceutically acceptable salts thereof , preferably the SGLT2 inhibitor is empagliflozin.

28. The method according to any one of items 26 to 27, wherein the PPAR agonist is selected from the group comprising lanifibranor, a deuterated form of lanifibranor and pharmaceutically acceptable salts thereof.

29. The method according to item 28, 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, preferably 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.

30. The method according to any one of items 26 to 29, wherein the patient is diagnosed with a liver disease.

31. The method according to item 30, wherein the liver disease is selected from liver fibrosis, liver steatosis, fatty liver disease, acute decompensation, 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), diabetes, autoimmune cholangitis, primary biliary cholangitis, primary sclerosing cholangitis, autoimmune cholangiopathy, hepatocarcinoma and a combination of these diseases.

32. The method according to any one of items 26 to 31, wherein blood disorders consist in a reduction in the amount of at least one biomarker compared to the reference amount of said at least one biomarker, wherein said at least one biomarker is selected from: hemoglobin, ferritin, haptoglobin, hematocrit, transferrin, vitamin B12, and a combination thereof.

33. The method according to item 32, wherein the reduction in the amount of at least one biomarker is equal or greater than 5% compared to the reference amount of at least one biomarker of said patient.

34. The method according to any one of items 26 to 33, wherein said patient:

a. is diagnosed with one or more of the conditions selected from the group consisting of overweight, obesity, visceral obesity and abdominal obesity; or
b. displays at least one of the following conditions:
    a. being over the age of 40 years;
    b. a poor iron absorption;
    c. a body mass index equal to or greater than 30 kg/m2;
    d. a reference amount of HbA1c equal to or greater than 7.0 %;
    e. a reference amount of hemoglobin equal to or below than 140 g/L;
    f. diagnosed with one of the following diseases: diabetes, dyslipidemia, cardiovascular diseases, cancer, polycystic ovary syndrome, acute lung injury, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, insulin resistance, obesity, diseases linked to endothelial dysfunction, atherosclerosis, myocardial infarction, hypertension, cerebrovascular problems, inflammatory diseases such as rheumatoid arthritis, chronic kidney disease, a pulmonary fibrotic disorder such as idiopathic pulmonary fibrosis, systemic sclerosis and neurodegeneration such as Alzheimer's disease or Parkinson's disease;
    g. diagnosed with a liver disease;
    h. diagnosed with non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), metabolic-associated fatty liver disease (MAFLD), metabolic-associated steatohepatitis (MASH) and/or diabetes.

35. The method according to any one of items 26 to 34, wherein said patient further displays at least one of the following conditions:

a. aspartate aminotransferase (AST) amount greater than or equal to 10.0 U/L;
b. alanine aminotransferase (ALT) amount greater than or equal to 10.0 U/L;
c. gamma glutamyl transferase (GGT) amount greater than or equal to 3.0 U/L;
d. fasting blood glucose amount greater than or equal to 4.0 mmol/L;
e. HDL-cholesterol blood amount below than or equal to 2.50 mmol/L;
f. triglyceride blood amount greater than or equal to 0.70 mmol/L;
g. ferritin amount greater than or equal to 6.0 µg/L;
h. a systolic blood pressure greater than or equal to 95 mm Hg and a diastolic blood pressure greater than or equal to 60 mm Hg;
i. ratio visceral adipose tissue (VAT)/ subcutaneous adipose tissue (SAT) (VAT/SAT) greater than or equal to 0.30;
j. cT1 amount greater than or equal to 700 ms.

36. The method according to any one of items 26 to 35, wherein said prevention comprises the administration in combination or alternation or sequentially of the PPAR agonist and the SGLT2 inhibitor.

37. The method according to any one of items 26 to 36, wherein the patient is treated or is planned to be treated with a PPAR agonist and wherein the first dose of SGLT2 inhibitor is:

a. administered at least one day after the start of the treatment with the PPAR agonist; or

b. administered at the same time as the first dose of the treatment with the PPAR agonist; or

c. administered at least one day before the start of the treatment with the PPAR agonist.

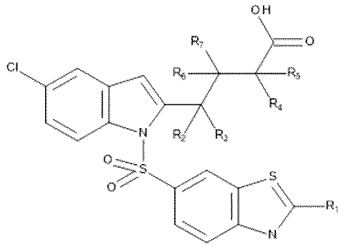
38. The method according to any one of items 26 to 37, wherein said PPAR agonist is lanifibranor a deuterated form of lanifibranor or a pharmaceutically acceptable salt thereof and said SGLT2 inhibitor is empagliflozin or a pharmaceutically acceptable salt thereof.

39. A method for reducing or preventing the discontinuation of a treatment with a PPAR agonist in a patient treated with such PPAR agonist, said method comprising administering to said patient a SGLT2 inhibitor.

40. The method according to item 39, wherein the SGLT2 inhibitor is selected from the group comprising canaglifozin, dapagliflozin, remoglifozin, sergliflozin, empagliflozin, ipragliflozin, tofogliflozin, luseogliflozin, sotagliflozin, ertuglifozin, bexagliflozin, henagliflozin, janagliflozin, tianagliflozin, and pharmaceutically acceptable salts thereof, preferably the SGLT2 inhibitor is empagliflozin.

41. The method according to any one of items 39 to 40, wherein the PPAR agonist is selected from the group comprising lanifibranor, a deuterated form of lanifibranor and pharmaceutically acceptable salts thereof.

42. The method according to item 41, 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, preferably 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.

43. The method according to any one of items 39 to 42, wherein the patient is diagnosed with a liver disease.

44. The method according to item 43, wherein the liver disease is selected from liver fibrosis, liver steatosis, fatty liver disease, acute decompensation, 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), diabetes, autoimmune cholangitis, primary biliary cholangitis, primary sclerosing cholangitis, autoimmune cholangiopathy, hepatocarcinoma and a combination of these diseases.

45. The method according to any one of items 39 to 44, wherein blood disorders consist in a reduction in the amount of at least one biomarker compared to the reference amount of said at least one biomarker, wherein said at least one biomarker is selected from : hemoglobin, ferritin, haptoglobin, hematocrit, transferrin, vitamin B12 and a combination thereof.

46. The method according to item 45, wherein the reduction in the amount of at least one biomarker is equal or greater than 5% compared to the reference amount of at least one biomarker of said patient.

47. The method according to any one of items 39 to 46, wherein said patient:

a. is diagnosed with of one or more of the conditions selected from the group consisting of overweight, obesity, visceral obesity and abdominal obesity; or

b. displays at least one of the following conditions:

(a) being over the age of 40 years;

(b) a poor iron absorption;

(c) a body mass index equal to or greater than 30 kg/m2;

(d) a reference amount of HbA1c equal to or greater than 7.0 %;

(e) a reference amount of hemoglobin equal to or below than 140 g/L;

(f) diagnosed with one of the following diseases: diabetes, dyslipidemia, cardiovascular diseases, cancer, polycystic ovary syndrome, acute lung injury, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, insulin resistance, obesity, diseases linked to endothelial dysfunction, atherosclerosis, myocardial infarction, hypertension, cerebrovascular problems, inflammatory diseases such as rheumatoid arthritis, chronic kidney disease, a pulmonary fibrotic disorder such as idiopathic pulmonary fibrosis, systemic sclerosis and neurodegeneration such as Alzheimer's disease or Parkinson's disease;

(g) diagnosed with a liver disease;

(h) diagnosed with non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), metabolic-associated fatty liver disease (MAFLD), and/or metabolic-associated steatohepatitis (MASH) and/or diabetes.

48. The method according to any one of items 39 to 47, wherein said patient further displays at least one of the following conditions:

a. aspartate aminotransferase (AST) amount greater than or equal to 10.0 U/L;

b. alanine aminotransferase (ALT) amount greater than or equal to 10.0 U/L;

c. gamma glutamyl transferase (GGT) amount greater than or equal to 3.0 U/L;

d. fasting blood glucose amount greater than or equal to 4.0 mmol/L;

e. HDL-cholesterol blood amount below than or equal to 2.50 mmol/L;

f. triglyceride blood amount greater than or equal to 0.70 mmol/L;

g. ferritin amount greater than or equal to 6.0 µg/L;

h. a systolic blood pressure greater than or equal to 95 mm Hg and a diastolic blood pressure greater than or equal to 60 mm Hg;

i. ratio visceral adipose tissue (VAT)/ subcutaneous adipose tissue (SAT) (VAT/SAT) greater than or equal to 0.30;

j. cT1 amount greater than or equal to 700 ms.

49. The method according to any one of items 39 to 48, wherein said prevention comprises the administration in combination or alternation or sequentially of the PPAR agonist and the SGLT2 inhibitor.

50. The method according to any one of items 39 to 49, wherein the patient is treated or is planned to be treated with a PPAR agonist and wherein the first dose of SGLT2 inhibitor is:

a. administered at least one day after the start of the treatment with the PPAR agonist; or

b. administered at the same time as the first dose of the treatment with the PPAR agonist; or

c. administered at least one day before the start of the treatment with the PPAR agonist.

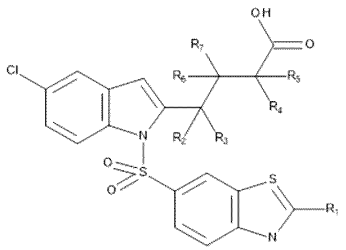
51. The method according to any one of items 39 to 50, wherein said PPAR agonist is lanifibranor a deuterated form of lanifibranor or a pharmaceutically acceptable salt thereof and said SGLT2 inhibitor is empagliflozin or a pharmaceutically acceptable salt thereof.

52. A pharmaceutical composition comprising a sodium glucose transporter 2 (SGLT2) inhibitor for use for preventing or delaying the clinical complications of blood disorders in a patient having been treated, treated or planned to be treated with a PPAR agonist.

53. The pharmaceutical composition for use according to item 52, wherein the SGLT2 inhibitor is selected from the group comprising canaglifozin, dapagliflozin, remoglifozin, sergliflozin, empagliflozin, ipragliflozin, tofogliflozin, luseogliflozin, sotagliflozin, ertuglifozin, bexagliflozin, henagliflozin, janagliflozin, tianagliflozin, and A pharmaceutically acceptable salts thereof, preferably the SGLT2 inhibitor is empagliflozin.

54. The pharmaceutical composition for use according to any one of items 52 to 53, wherein the PPAR agonist is selected from the group comprising lanifibranor, a deuterated form of lanifibranor and pharmaceutically acceptable salts thereof.

55. The pharmaceutical composition for use according to item 54, 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, preferably 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.

56. The pharmaceutical composition for use according to any one of items 52 to 55, wherein the patient is diagnosed with a liver disease.

57. The pharmaceutical composition for use according to item 56, wherein the liver disease is selected from liver fibrosis, liver steatosis, fatty liver disease, acute decompensation, 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), diabetes, autoimmune cholangitis, primary biliary cholangitis, primary sclerosing cholangitis, autoimmune cholangiopathy, hepatocarcinoma and a combination of these diseases.

58. The pharmaceutical composition for use according to any one of items 52 to 57, wherein blood disorders consist in a reduction in the amount of at least one biomarker compared to the reference amount of said at least one biomarker, wherein said at least one biomarker is selected from: hemoglobin, ferritin, haptoglobin, hematocrit, transferrin, vitamin B12, and a combination thereof.

59. The pharmaceutical composition for use according to item 58, wherein the reduction in the amount of at least one biomarker is equal or greater than 5% compared to the reference amount of at least one biomarker of said patient.

60. The pharmaceutical composition for use according to any one of items 52 to 59, wherein said patient:

a. is diagnosed with one or more of the conditions selected from the group consisting of overweight, obesity, visceral obesity and abdominal obesity; or

b. displays at least one of the following conditions:

(a) being over the age of 40 years;

(b) a poor iron absorption;

(c) a body mass index equal to or greater than 30 kg/m2;

(d) a reference amount of HbA1c equal to or greater than 7.0 %;

(e) a reference amount of hemoglobin equal to or below than 140 g/L;

(f) diagnosed with one of the following diseases: diabetes, dyslipidemia, cardiovascular diseases, cancer, polycystic ovary syndrome, acute lung injury, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, insulin resistance, obesity, diseases linked to endothelial dysfunction, atherosclerosis, myocardial infarction, hypertension, cerebrovascular problems, inflammatory diseases such as rheumatoid arthritis, chronic kidney disease, a pulmonary fibrotic disorder

such as idiopathic pulmonary fibrosis, systemic sclerosis and neurodegeneration such as Alzheimer's disease or Parkinson's disease;

(g) diagnosed with a liver disease;

(h) diagnosed with non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), metabolic-associated fatty liver disease (MAFLD), metabolic-associated steatohepatitis (MASH) and/or diabetes.

61. The pharmaceutical composition for use according to any one of items 52 to 60, wherein said patient further displays at least one of the following conditions:

a. aspartate aminotransferase (AST) amount greater than or equal to 10.0 U/L;
b. alanine aminotransferase (ALT) amount greater than or equal to 10.0 U/L;
c. gamma glutamyl transferase (GGT) amount greater than or equal to 3.0 U/L;
d. fasting blood glucose amount greater than or equal to 4.0 mmol/L;
e. HDL-cholesterol blood amount below than or equal to 2.50 mmol/L;
f. triglyceride blood amount greater than or equal to 0.70 mmol/L;
g. ferritin amount greater than or equal to 6.0 µg/L;
h. a systolic blood pressure greater than or equal to 95 mm Hg and a diastolic blood pressure greater than or equal to 60 mm Hg;
i. ratio visceral adipose tissue (VAT)/ subcutaneous adipose tissue (SAT) (VAT/SAT) greater than or equal to 0.30;
j. cT1 amount greater than or equal to 700 ms.

62. The pharmaceutical composition for use according to any one of items 52 to 61, wherein said prevention comprises the administration in combination or alternation or sequentially of the PPAR agonist and the SGLT2 inhibitor.

63. The pharmaceutical composition for use according to any one of items 52 to 62, wherein the patient is treated or is planned to be treated with a PPAR agonist and wherein the first dose of SGLT2 inhibitor is:

a. administered at least one day after the start of the treatment with the PPAR agonist; or

b. administered at the same time as the first dose of the treatment with the PPAR agonist; or

c. administered at least one day before the start of the treatment with the PPAR agonist.

64. The pharmaceutical composition for use according to any one of items 52 to 63, wherein said PPAR agonist is lanifibranor a deuterated form of lanifibranor or a pharmaceutically acceptable salt thereof and said SGLT2 inhibitor is empagliflozin or a pharmaceutically acceptable salt thereof.

65. The pharmaceutical composition for use according to any one of items 52 to 64, wherein said PPAR agonist and said SGLT2 inhibitor are in the same and unique pharmaceutical composition.

66. The pharmaceutical composition for use according to any one of items 52 to 64, wherein said PPAR agonist and said SGLT2 inhibitor are in two separate and distinct pharmaceutical compositions.

67. SGLT2 inhibitor for use for the prevention of the reduction in the amount of hemoglobin in a patient having been treated, treated or planned to be treated with a PPAR agonist.

68. SGLT2 inhibitor for use for the reduction or prevention of the discontinuation of a treatment with a PPAR agonist in a patient treated with such PPAR agonist.

69. SGLT2 inhibitor for use for weight reduction or reduction of body fat, or for preventing an increase of body weight or for attenuating an increase of body weight in a patient treated for a liver disease, said patient having been treated, treated or planned to be treated with a PPAR agonist.

70. A pharmaceutical composition comprising a SGLT2 inhibitor for use for the prevention of the reduction in the amount of hemoglobin in a patient having been treated, treated or planned to be treated with a PPAR agonist.

71. A pharmaceutical composition comprising a SGLT2 inhibitor for use for the reduction or prevention of the discontinuation of a treatment with a PPAR agonist in a patient treated with such PPAR agonist.

72. A pharmaceutical composition comprising a SGLT2 inhibitor for use for the weight reduction or reduction of body fat, or for preventing an increase of body weight or for attenuating an increase of body weight in a patient treated for liver disease, said patient having been treated, treated or planned to be treated with a PPAR agonist.

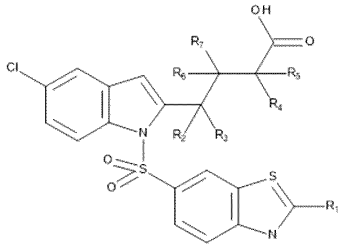
73. A method for reducing weight or body fat, or for preventing an increase of body weight or for attenuating an increase of body weight in a patient treated for a liver disease, said method comprising administering to said patient a SGLT2 inhibitor and a PPAR agonist.

74. The method according to item 73, wherein said SGLT2 inhibitor and said PPAR agonist are administered in combination or alternation or sequentially to the patient.

75. The method according to any one of items 73 to 74, wherein the SGLT2 inhibitor is selected from the group comprising canaglifozin, dapagliflozin, remoglifozin, sergliflozin, empagliflozin, ipragliflozin, tofogliflozin, luseogliflozin, sotagliflozin, ertuglifozin, bexagliflozin, henagliflozin, janagliflozin, tianagliflozin, and a pharmaceutically acceptable salt thereof, preferably the SGLT2 inhibitor is empagliflozin.

76. The method according to any one of items 73 to 75, wherein the PPAR agonist is selected from the group comprising lanifibranor, a deuterated form of lanifibranor and pharmaceutically acceptable salts thereof.

77. The method according to item 76, 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, preferably 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.

78. The method according to any one of items 73 to 77, wherein the liver disease is selected from liver fibrosis, liver steatosis, fatty liver disease, acute decompensation, 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), diabetes, autoimmune cholangitis, primary biliary cholangitis, primary sclerosing cholangitis, autoimmune cholangiopathy, hepatocarcinoma and a combination of these diseases.

79. The method according to any one of items 73 to 78, wherein said patient:

a. is diagnosed with one or more of the conditions selected from the group consisting of overweight, obesity, visceral obesity and abdominal obesity; or

b. displays at least one of the following conditions:

(a) being over the age of 40 years;

(b) a poor iron absorption;

(c) a body mass index equal to or greater than 30 kg/m2;

(d) a reference amount of HbA1c equal to or greater than 7.0 %;

(e) a reference amount of hemoglobin equal to or below than 140 g/L;

(f) diagnosed with one of the following diseases: diabetes, dyslipidemia, cardiovascular diseases, cancer, polycystic ovary syndrome, acute lung injury, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, insulin resistance, obesity, diseases linked to endothelial dysfunction, atherosclerosis, myocardial

infarction, hypertension, cerebrovascular problems, inflammatory diseases such as rheumatoid arthritis, chronic kidney disease, a pulmonary fibrotic disorder such as idiopathic pulmonary fibrosis, systemic sclerosis and neurodegeneration such as Alzheimer's disease or Parkinson's disease;

(g) diagnosed with a liver disease;

(h) diagnosed with non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), metabolic-associated fatty liver disease (MAFLD), metabolic-associated steatohepatitis (MASH) and/or diabetes.

80. The method according to any one of items 73 to 79, wherein said patient further displays at least one of the following conditions:

a. aspartate aminotransferase (AST) amount greater than or equal to 10.0 U/L;
b. alanine aminotransferase (ALT) amount greater than or equal to 10.0 U/L;
c. gamma glutamyl transferase (GGT) amount greater than or equal to 3.0 U/L;
d. fasting blood glucose amount greater than or equal to 4.0 mmol/L;
e. HDL-cholesterol blood amount below than or equal to 2.50 mmol/L;
f. triglyceride blood amount greater than or equal to 0.70 mmol/L;
g. ferritin amount greater than or equal to 6.0 µg/L;
h. a systolic blood pressure greater than or equal to 95 mm Hg and a diastolic blood pressure greater than or equal to 60 mm Hg;
i. ratio visceral adipose tissue (VAT)/ subcutaneous adipose tissue (SAT) (VAT/SAT) greater than or equal to 0.30;
j. cT1 amount greater than or equal to 700 ms.

81. The method according to any one of items 73 to 80, wherein a first dose of SGLT2 inhibitor is:

a. administered at least one day after administration of the PPAR agonist; or
b. administered at the same time as a first dose of the PPAR agonist; or
c. administered at least one day before the start of the administration of the PPAR agonist.

82. The method according to any one of items 73 to 81, wherein said PPAR agonist and said SGLT2 inhibitor are in the same and unique pharmaceutical composition.

83. The method according to any one of items 73 to 81, wherein said PPAR agonist and said SGLT2 inhibitor are in two separate and distinct pharmaceutical compositions.

84. The method according to any one of items 73 to 83, wherein said PPAR agonist is lanifibranor a deuterated form of lanifibranor or a pharmaceutically acceptable salt thereof, and said SGLT2 inhibitor is empagliflozin or a pharmaceutically acceptable salt thereof.

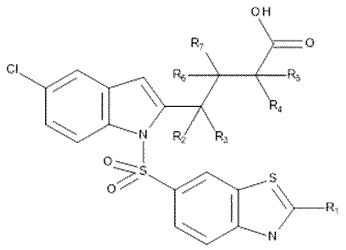
85. Sodium glucose transporter 2 (SGLT2) inhibitor for use for preventing or delaying anaemia or clinical complications of anaemia in a patient having been treated, treated or planned to be treated with a PPAR agonist.

86. The SGLT2 inhibitor for use according to item 85, wherein the SGLT2 inhibitor is selected from the group comprising canaglifozin, dapagliflozin, remoglifozin, sergliflozin, empagliflozin, ipragliflozin, tofogliflozin, luseogliflozin, sotagliflozin, ertuglifozin, bexagliflozin, henagliflozin, janagliflozin, tianagliflozin, and pharmaceutically acceptable salts thereof.

87. The SGLT2 inhibitor for use according to item 85 or item 86, wherein the SGLT2 inhibitor is empagliflozin and pharmaceutically acceptable salts thereof.

88. The SGLT2 inhibitor for use according to any one of items 85 to 87, wherein the PPAR agonist is selected from the group comprising lanifibranor, a deuterated form of lanifibranor and pharmaceutically acceptable salts thereof.

89. The SGLT2 inhibitor for use according to item 88, 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, preferably 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.

90. The SGLT2 inhibitor for use according to any one of items 85 to 89, wherein the patient is diagnosed with a liver disease.

91. The SGLT2 inhibitor for use according to item 90, wherein the liver disease is selected from liver fibrosis, liver steatosis, fatty liver disease, acute decompensation, 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), diabetes, autoimmune cholangitis, primary biliary cholangitis, primary sclerosing cholangitis, autoimmune cholangiopathy, hepatocarcinoma and a combination of these diseases.

92. The SGLT2 inhibitor for use according to any one of items 85 to 91, wherein anaemia or clinical complications of anaemia consists in a reduction in the amount of at least one biomarker compared to the reference amount of said at least one biomarker, wherein said at least one biomarker is selected from: hemoglobin, ferritin, haptoglobin, hematocrit, transferrin, vitamin B12 and a combination thereof.

93. The SGLT2 inhibitor for use according to item 92, wherein the reduction in the amount of at least one biomarker is equal or greater than 5% compared to the reference amount of at least one biomarker of said patient.

94. The SGLT2 inhibitor for use according to any one of items 85 to 93, wherein said patient:

a. is diagnosed with one or more conditions selected from the group consisting of overweight, obesity, visceral obesity and abdominal obesity; or
b. displays at least one of the following conditions:
    a. being over the age of 40 years;
    b. a poor iron absorption;
    c. a body mass index equal to or greater than 30 kg/m^2;
    d. a reference amount of HbA1c equal to or greater than 7.0 %;
    e. a reference amount of hemoglobin equal or below than 140 g/L;
    f. diagnosed with one of the following diseases: diabetes, dyslipidemia, cardiovascular diseases, cancer, polycystic ovary syndrome, acute lung injury, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, insulin resistance, obesity, diseases linked to endothelial dysfunction, atherosclerosis, myocardial infarction, hypertension, cerebrovascular problems, inflammatory diseases such as rheumatoid arthritis, chronic kidney disease, a pulmonary fibrotic disorder such as idiopathic pulmonary fibrosis, systemic sclerosis and neurodegeneration such as Alzheimer's disease or Parkinson's disease;
    g. diagnosed with a liver disease;
    h. diagnosed with non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), metabolic-associated fatty liver disease (MAFLD), metabolic-associated steatohepatitis (MASH) and/or diabetes.

95. The SGLT2 inhibitor for use according to any one of items 85 to 94, wherein said patient further displays at least one of the following conditions:

a. aspartate aminotransferase (AST) amount greater than or equal to 10.0 U/L;
b. alanine aminotransferase (ALT) amount greater than or equal to 10.0 U/L;
c. gamma glutamyl transferase (GGT) amount greater than or equal to 3.0 U/L;
d. fasting blood glucose amount greater than or equal to 4.0 mmol/L;

e. HDL-cholesterol blood amount below than or equal to 2.50 mmol/L;
f. triglyceride blood amount greater than or equal to 0.70 mmol/L;
g. ferritin amount greater than or equal to 6.0 µg/L;
h. a systolic blood pressure greater than or equal to 95 mm Hg and a diastolic blood pressure greater than or equal to 60 mm Hg;
i. ratio visceral adipose tissue (VAT)/ subcutaneous adipose tissue (SAT) (VAT/SAT) greater than or equal to 0.30;
j. cT1 amount greater than or equal to 700 ms.

96. The SGLT2 inhibitor for use according to any one of items 85 to 95, wherein said prevention comprises the administration in combination or alternation or sequentially of the PPAR agonist and the SGLT2 inhibitor.

97. The SGLT2 inhibitor for use according to any one of items 85 to 96, wherein the patient is treated or is planned to be treated with a PPAR agonist and the first dose of SGLT2 inhibitor is:

a. administered at least one day after the start of the treatment with the PPAR agonist; or

b. administered at the same time as the first dose of the treatment with the PPAR agonist; or

c. administered at least one day before the start of the treatment with the PPAR agonist.

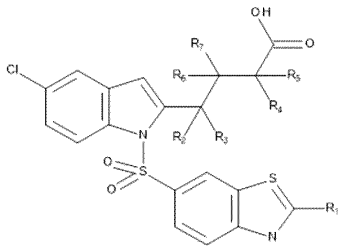
98. A method for preventing or delaying anaemia or clinical complications of anaemia, in patient having been treated, treated or being planned to be treated with a PPAR agonist, said method comprising administering to said patient a suitable dosage of a SGLT2 inhibitor.

99. The method according to item 98, wherein the SGLT2 inhibitor is selected from the group comprising canaglifozin, dapagliflozin, remoglifozin, sergliflozin, empagliflozin, ipragliflozin, tofogliflozin, luseogliflozin, sotagliflozin, ertuglifozin, bexagliflozin, henagliflozin, janagliflozin, tianagliflozin, and a pharmaceutically acceptable salt thereof.

100. The method according to item 99, wherein the SGLT2 inhibitor is empagliflozin and a pharmaceutically acceptable salt thereof.

101. The method according to any one of items 98 to 100, wherein the PPAR agonist is selected from the group comprising lanifibranor, a deuterated form of lanifibranor and pharmaceutically acceptable salts thereof.

102. The method according to item 101, 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, preferably 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.

103. The method according to any one of items 98 to 102, wherein the patient is diagnosed with a liver disease.

104. The method according to item 103, wherein the liver disease is selected from liver fibrosis, liver steatosis, fatty liver disease, acute decompensation, 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), diabetes, autoimmune cholangitis, primary biliary cholangitis, primary sclerosing cholangitis, autoimmune cholangiopathy, hepatocarcinoma and a combination of these diseases.

105. The method according to any one of items 98 to 104, wherein anaemia or clinical complications of anaemia consist in a reduction in the amount of at least one biomarker compared to the reference amount of said at least one biomarker, wherein said at least one biomarker is selected from: hemoglobin, ferritin, haptoglobin, unsaturated iron binding capacity, iron, lactate dehydrogenase, hematocrit, transferrin, vitamin B12, vitamin B9 and a combination thereof.

106. The method according to item 105, wherein the reduction in the amount of at least one biomarker is equal or greater than 5% compared to the reference amount of at least one biomarker of said patient.

107. The method according to any one of items 98 to 106, wherein said patient:

a. is diagnosed with one or more of the conditions selected from the group consisting of overweight, obesity, visceral obesity and abdominal obesity; or
b. displays at least one of the following conditions:
    a. being over the age of 40 years;
    b. a poor iron absorption;
    c. a body mass index equal to or greater than 30 kg/m2;

d. a reference amount of HbA1c equal to or greater than 7.0 %;
e. a reference amount of hemoglobin equal to or below than 140 g/L;
f. diagnosed with one of the following diseases: diabetes, dyslipidemia, cardiovascular diseases, cancer, polycystic ovary syndrome, acute lung injury, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, insulin resistance, obesity, diseases linked to endothelial dysfunction, atherosclerosis, myocardial infarction, hypertension, cerebrovascular problems, inflammatory diseases such as rheumatoid arthritis, chronic kidney disease, a pulmonary fibrotic disorder such as idiopathic pulmonary fibrosis, systemic sclerosis and neurodegeneration such as Alzheimer's disease or Parkinson's disease;
g. diagnosed with a liver disease;
h. diagnosed with non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), metabolic-associated fatty liver disease (MAFLD), metabolic-associated steatohepatitis (MASH) and/or diabetes.

108. The method according to any one of items 98 to 107, wherein said patient further displays at least one of the following conditions:

a. aspartate aminotransferase (AST) amount greater than or equal to 10.0 U/L;
b. alanine aminotransferase (ALT) amount greater than or equal to 10.0 U/L;
c. gamma glutamyl transferase (GGT) amount greater than or equal to 3.0 U/L;
d. fasting blood glucose amount greater than or equal to 4.0 mmol/L;
e. HDL-cholesterol blood amount below than or equal to 2.50 mmol/L;
f. triglyceride blood amount greater than or equal to 0.70 mmol/L;
g. ferritin amount greater than or equal to 6.0 µg/L;
h. a systolic blood pressure greater than or equal to 95 mm Hg and a diastolic blood pressure greater than or equal to 60 mm Hg;
i. ratio visceral adipose tissue (VAT)/ subcutaneous adipose tissue (SAT) (VAT/SAT) greater than or equal to 0.30;
j. cT1 amount greater than or equal to 700 ms.

109. The method according to any one of items 98 to 108, wherein said SGLT2 inhibitor and said PPAR agonist are administered in combination or alternation or sequentially of the PPAR agonist and the SGLT2 inhibitor.

110. The method according to any one of items 98 to 109, wherein the patient is treated or is planned to be treated with a PPAR agonist and wherein the first dose of SGLT2 inhibitor is:

a. administered at least one day after the start of the treatment with the PPAR agonist; or

b. administered at the same time as the first dose of the treatment with the PPAR agonist; or

c. administered at least one day before the start of the treatment with the PPAR agonist.

111. The method according to any one of items 98 to 110, wherein said PPAR agonist is lanifibranor a deuterated form of lanifibranor or a pharmaceutically acceptable salt thereof and said SGLT2 inhibitor is empagliflozin or a pharmaceutically acceptable salt thereof.

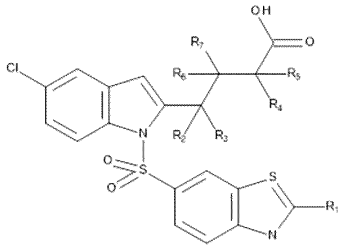
112. A pharmaceutical composition comprising a sodium glucose transporter 2 (SGLT2) inhibitor for use for preventing or delaying anaemia or clinical complications of anaemia in a patient having been treated, treated or planned to be treated with a PPAR agonist.

113. The pharmaceutical composition for use according to item 112, wherein the SGLT2 inhibitor is selected from the group comprising canaglifozin, dapagliflozin, remoglifozin, sergliflozin, empagliflozin, ipragliflozin, tofogliflozin, luseogliflozin, sotagliflozin, ertuglifozin, bexagliflozin, henagliflozin, janagliflozin, tianagliflozin, and pharmaceutically acceptable salts thereof.

114. The pharmaceutical composition for use according to item 112 or item 113, wherein the SGLT2 inhibitor is empagliflozin and pharmaceutically acceptable salts thereof.

115. The pharmaceutical composition for use according to any one of items 112 to 114, wherein the PPAR agonist is selected from the group comprising lanifibranor, a deuterated form of lanifibranor and pharmaceutically acceptable salts thereof.

116. The pharmaceutical composition for use according to item 115, 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, preferably 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.

117. The pharmaceutical composition for use according to any one of items 112 to 116, wherein the patient is diagnosed with a liver disease.

118. The pharmaceutical composition for use according to item 117, wherein the liver disease is selected from liver fibrosis, liver steatosis, fatty liver disease, acute decompensation, 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), diabetes, autoimmune cholangitis, primary biliary cholangitis, primary sclerosing cholangitis, autoimmune cholangiopathy, hepatocarcinoma and a combination of these diseases.

119. The pharmaceutical composition for use according to any one of items 112 to 118, wherein blood disorders consist in a reduction in the amount of at least one biomarker compared to the reference amount of said at least one biomarker, wherein said at least one biomarker is selected from: hemoglobin, ferritin, haptoglobin, hematocrit, transferrin, vitamin B12, and a combination thereof.

120. The pharmaceutical composition for use according to item 119, wherein the reduction in the amount of at least one biomarker is equal or greater than 5% compared to the reference amount of at least one biomarker of said patient.

121. The pharmaceutical composition for use according to any one of items 112 to 120, wherein said patient:

a. is diagnosed with one or more of the conditions selected from the group consisting of overweight, obesity, visceral obesity and abdominal obesity; or

b. displays at least one of the following conditions:

(a) being over the age of 40 years;

(b) a poor iron absorption;

(c) a body mass index equal to or greater than 30 kg/m2;

(d) a reference amount of HbA1c equal to or greater than 7.0 %;

(e) a reference amount of hemoglobin equal to or below than 140 g/L;

(f) diagnosed with one of the following diseases: diabetes, dyslipidemia, cardiovascular diseases, cancer, polycystic ovary syndrome, acute lung injury, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, insulin resistance, obesity, diseases linked to endothelial dysfunction, atherosclerosis, myocardial infarction, hypertension, cerebrovascular problems, inflammatory diseases such as rheumatoid arthritis, chronic kidney disease, a pulmonary fibrotic disorder such as idiopathic pulmonary fibrosis, systemic sclerosis and neurodegeneration such as Alzheimer's disease or Parkinson's disease;

(g) diagnosed with a liver disease;

(h) diagnosed with non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), metabolic-associated fatty liver disease (MAFLD), metabolic-associated steatohepatitis (MASH) and/or diabetes.

122. The pharmaceutical composition for use according to any one of items 112 to 121, wherein said patient further displays at least one of the following conditions:

a. aspartate aminotransferase (AST) amount greater than or equal to 10.0 U/L;
b. alanine aminotransferase (ALT) amount greater than or equal to 10.0 U/L;
c. gamma glutamyl transferase (GGT) amount greater than or equal to 3.0 U/L;
d. fasting blood glucose amount greater than or equal to 4.0 mmol/L;
e. HDL-cholesterol blood amount below than or equal to 2.50 mmol/L;
f. triglyceride blood amount greater than or equal to 0.70 mmol/L;
g. ferritin amount greater than or equal to 6.0 µg/L;
h. a systolic blood pressure greater than or equal to 95 mm Hg and a diastolic blood pressure greater than or equal to 60 mm Hg;
i. ratio visceral adipose tissue (VAT)/ subcutaneous adipose tissue (SAT) (VAT/SAT) greater than or equal to 0.30;
j. cT1 amount greater than or equal to 700 ms.

123. The pharmaceutical composition for use according to any one of items 112 to 122, wherein said prevention comprises the administration in combination or alternation or sequentially of the PPAR agonist and the SGLT2 inhibitor.

124. The pharmaceutical composition for use according to any one of items 112 to 123, wherein the patient is treated or is planned to be treated with a PPAR agonist and wherein the first dose of SGLT2 inhibitor is:

a. administered at least one day after the start of the treatment with the PPAR agonist; or
b. administered at the same time as the first dose of the treatment with the PPAR agonist; or
c. administered at least one day before the start of the treatment with the PPAR agonist.

125. The pharmaceutical composition for use according to any one of items 112 to 124, wherein said PPAR agonist is lanifibranor a deuterated form of lanifibranor or a pharmaceutically acceptable salt thereof and said SGLT2 inhibitor is empagliflozin or a pharmaceutically acceptable salt thereof.

126. The pharmaceutical composition for use according to any one of items 112 to 125, wherein said PPAR agonist and said SGLT2 inhibitor are in the same and unique pharmaceutical composition.

127. The pharmaceutical composition for use according to any one of items 112 to 126, wherein said PPAR agonist and said SGLT2 inhibitor are in two separate and distinct pharmaceutical compositions.

EXAMPLES

Abbreviations

ALT: alanine aminotransferase

AST: aspartate aminotransferase

GGT: gamma glutamyl transferase

HbA1c: glycated hemoglobin

VAT: visceral adipose tissue

SAT: subcutaneous adipose tissue

SBP: Systolic blood pressure

DBP: Diastolic blood pressure

MRI PDFF: Magnetic Resonance Imaging-Proton Density Fat Fraction

MRI: Magnetic Resonance Imaging

HDL-C: HDL-cholesterol

HOMA-IR: Homeostatic Model Assessment – Insulin resistance

MMRM: Mixed model repeated measure

LS mean: Least squares means

Example 1: Effect on SGLT2 inhibitor (empagliflozin) in the prevention of blood disorders in patients treated with a PPAR agonist (lanifibranor).

A multinational, multicenter, randomized, double-blind, placebo-controlled, three-parallel groups, phase 2 study was conducted to assess the safety of lanifibranor plus empagliflozin as compared to placebo and to lanifibranor alone in patients with non-alcoholic steatohepatitis (NASH) and type 2 diabetes mellitus (T2DM), for 24-week treatment study followed by a 4 weeks post-treatment follow-up visit.

The objective of this study was to identify any potential positive effect of the combination of lanifibranor with an SGLT2 inhibitor on the tolerability of the combination treatment. The study assessed the impact on safety (including body weight changes), metabolic parameters, inflammatory markers, body composition, liver function, and improvement in hepatic steatosis and fibrosis.

Safety was assessed based on the measurement of hemoglobin and ferritin at the end of the 24-week treatment.

The patients recruited in the study were adult patients diagnosed with non-cirrhotic NASH and T2DM. The diagnosis of NASH was based on the histology of a prior liver

biopsy or assessed as high-risk NASH by using LiverMultiScan®. Exclusion of cirrhosis at Screening was based on histology or Non-Invasive Tests (NITs).

A total of 32 patients were randomized and treated in three groups with a ratio 1:1:1:

- Group 1 (10 patients): lanifibranor (800 mg orally once daily) plus empagliflozin (10mg orally once daily) for a total of 24 weeks.
- Group 2 (12 patients): lanifibranor (800 mg orally once daily) for a total of 24 weeks;
- Group 3 (10 patients): placebo for a total of 24 weeks;

On 32 patients:

- 100% of patients of group 1, 100% of patients of group 2 and 50% of patients of group 3 completed the 24-week treatment,
- 50% of patients of group 3 prematurely discontinued from study treatment.

Main inclusion criteria were:

- Male or female, aged over 18 years at the time of signing informed consent
- Diagnosis of NASH based on histology or cT1 equal to or greater than 875ms assessed by LiverMultiScan or cT1 equal to or greater than 825ms assessed by LiverMultiScan and hepatic fat content ≥ 10% assessed by MRI-PDFF at screening
- HbA1c at screening equal to or greater than 7.0% and equal to or below 10.0%, on diet alone, or on metformin treatment (equal to or higher than 1,000 mg/day) and/or dipeptidyl peptidase 4 inhibitor (DPP-IVi) therapy. Doses had no qualitative change for 3 months prior to informed consent. These medicines were continued at stable doses during the entire study.

Main exclusion criteria were:

- Documented causes of chronic liver disease other than NASH
- Histologically documented liver cirrhosis (fibrosis stage F4)
- History or current diagnosis of hepatocellular carcinoma (HCC)
- History of or planned liver transplant
- Documented history of human immunodeficiency virus (HIV) infection
- ALT or AST higher than 5 times upper limit of normal (ULN) at Screening
- Abnormal liver function as defined by central laboratory evaluation
- Amount of hemoglobin below 110 g/L (11 g/dL) in women and below 120 g/L (12 g/dL) in men
- Patient currently receiving any approved treatment for obesity or investigational treatment for NASH
- Current or recent history (less than 5 years) of significant alcohol addiction

- Administration of drugs known to produce hepatic steatosis in the 6 months prior to Screening
- Diabetes mellitus other than type 2
- Current treatment with glucagon-like peptide-1 receptor agonist (GLP-1RA), insulin or sulfonylurea
- Patients on pioglitazone in the last 12 months prior to Screening
- Body mass index (BMI) higher than 45 kg/m^2 at Screening
- Body weight change higher than 5% in the 3 months prior to Screening

1. Materials and methods:

Blood samples have been collected for each patient of the study at the following intervals: at visit 1 (screening visit: 6 weeks before treatment), at visit 2 (baseline visit: first administration of the treatment), at visit 3 (after 4-week treatment), at visit 4 (after 12-week treatment) and visit 5 (after 24-week treatment). Clinical laboratory tests for hemoglobin were performed using a spectrophotometry method. Clinical laboratory tests for ferritin were performed using electrochemiluminescence immunoassay. Anaemia has been assessed based on hemoglobin and ferritin measurements.

2. Results

The results are presented in Table 1.

Table 1: Effect on SGLT2 inhibitor (empagliflozin) in the prevention of anaemia in patients treated with a PPAR agonist (lanifibranor).

Treatment groups		Group 1: Empagliflozin plus Lanifibranor	Group 2: Lanifibranor	Group 3: Placebo
Hemoglobin absolute change at week 24 (g/L)	Mean ±SD[a]	0.5 ± 8.5 (10 patients)	-7.5 ± 6.7 (12 patients)	-3.0 ± 6.6 (9 patients)
Ferritin absolute change at week 24 (µg/L)	Mean ±SD[a]	-54.9 ± 42 (10 patients)	-85.1 ± 75 (12 patients)	-16.3 ± 62 (9 patients)
Ferritin absolute change at week 24 (µg/L)	LS mean[b1] *p<0.01, versus placebo (MMRM)	-66.2* (13 patients)	-76.4* (12 patients)	-1.8 (13 patients)
Transferrin absolute change at week 24 (g/L)	Mean ±SD[a]	0.16 ± 0.27 (10 patients)	0.06 ± 0.35 (12 patients)	-0.05 ± 0.30 (9 patients)
Haptoglobin absolute change at week 24 (g/L)	Mean ±SD[a]	-0.06 ± 0. 22 (9 patients)	-0.13 ± 0.35 (12 patients)	0.01 ± 0.52 (9 patients)
Vitamin B12 absolute change at week 24 (pmol/L)	Mean ±SD[a]	-94.7 ± 135.1 (9 patients)	-78.2 ± 157.5 (12 patients)	22.64 ± 58.85 (9 patients)

Hematocrit absolute change at week 24 (L/L)	Mean ±SD[a]	-0.01 ± 0.03 (10 patients)	-0.04 ± 0.02 (12 patients)	0.00 ± 0.02 (9 patients)

[a]: mean = descriptive mean. SD=Standard deviation.

[b1]: LS mean = means are computed based on Mixed Model Repeated Measure (MMRM) linear model

It can be seen from Table 1 that empagliflozin corrects the hemoglobin decrease observed in patients treated with lanifibranor (mean absolute increase of +0.5g/L for patients under empagliflozin plus lanifibranor versus decrease of -3.0g/L under placebo). Empagliflozin also corrects the level of ferritin, the level of transferrin, the level of haptoglobin, and the level of hematocrit observed in patients treated with lanifibranor.

SGLT2 inhibitor, in particular empagliflozin, thus allows preventing or delaying clinical complications of blood disorders, and in particular allows preventing or delaying anaemia, in a patients having been treated, treated or planned to be treated with a PPAR agonist, and in particular in a patients having been treated, treated or planned to be treated with lanifibranor.

Example 2: Effect on SGLT2 inhibitor (empagliflozin) in the prevention of weight gain in patients treated with a PPAR agonist (lanifibranor).

1. Materials and methods:

Body weight measurements:

Body weight will be measured in a fasting state at visit 1 (screening visit: 6 weeks before treatment), at visit 2 (baseline visit: first administration of the treatment), at visit 3 (after 4-week treatment), at visit 4 (after 12-week treatment) and visit 5 (after 24-week treatment). The body weight should be measured with an empty bladder, without shoes, and only wearing light clothing. Pockets should be emptied of heavy objects (i.e., keys, coins etc). Body weight has to be recorded with one decimal (kg or lb) and using the same digital scale throughout the study. The scale used in the study center will be calibrated according to the directions for use.

2. Results

The results are presented in Table 2.

Table 2: Effect on SGLT2 inhibitor (empagliflozin) in the prevention of weight gain in patients treated with a PPAR agonist (lanifibranor).

Treatment groups		Group 1: Empagliflozin plus Lanifibranor	Group 2: Lanifibranor	Group 3: Placebo
Weight relative changes (%) – week 12	Mean ±SD[a]	-0.76 ± 3.1 (11 patients)	2.01 ± 2.7 (12 patients)	-0.72 ± 2.0 (13 patients)
Weight relative changes (%) – week 24	Mean ±SD[a]	-0.06 ± 3.2 (10 patients)	3.55 ± 3.3 (12 patients)	-1.01 ± 2.1 (9 patients)

[a]: mean = descriptive mean. SD=Standard deviation.

It can be seen from Table 2 that SGLT2 inhibitor, and in particular empagliflozin corrects the weight gain observed in patients treated with lanifibranor. SGLT2 inhibitor, and in particular empagliflozin, thus allows preventing gain weight or compensating or neutralizing gain weight in patient under treatment with a PPAR agonist, and in particular with lanifibranor.

Example 3: Effect on SGLT2 inhibitor (empagliflozin) in the prevention of cardiovascular diseases in patients treated with a PPAR agonist (lanifibranor).

1. Materials and methods:
    a. Body composition measurements:

MRI assessments are performed at screening and Week 24 with the patient in fasted state (at least 2 hours after food or beverage). MRI assessment for body composition will include but is not limited to: L3 visceral adipose tissue (VAT)/ subcutaneous adipose tissue (SAT) and thigh SAT (left and right)

L3 VAT/SAT:

The cross-sectional area of VAT and the cross-sectional area of SAT are measured in the axial plane at the third lumbar vertebra (L3). 3D multi-echo gradient echo pulse sequences covering the abdomen are acquired and processed to provide an image of fat on which measurements are performed through the semi-automated delineation of the VAT and SAT areas. The output is measurements of VAT and SAT in cm^2.

Thigh SAT:

The cross-sectional area of SAT is measured in the thighs (each separately) in the axial plane at a location 20 cm inferior to the top of the femoral head. 3D multi-echo gradient echo pulse sequences covering the abdomen are acquired and processed to provide an image of fat on which measurement is performed through the semi-automated delineation of the SAT areas. The output is SAT in cm^2.

2. Results

The results are presented in Table 3.

Table 3: Effect on SGLT2 inhibitor (empagliflozin) in the prevention of cardiovascular diseases in patients treated with a PPAR agonist (lanifibranor).

Treatment groups		Group 1: Empagliflozin plus Lanifibranor	Group 2: Lanifibranor	Group 3: Placebo
Subcutaneous Adipose Tissue (SAT) absolute change from baseline – week 24	Mean ±SD[a]	24.61 ± 27.64 (7 patients)	22.17 ± 41.49 (9 patients)	-7.17 ± 15.09 (7 patients)
Visceral Adipose Tissue (VAT) absolute change from baseline– week 24	Mean ±SD[a]	-37.91 ± 53.97 (11 patients)	11.03 ± 32.09 (11 patients)	-10.54 ± 23.42 (8 patients)
Absolute change from baseline VAT/SAT ratio – week 24	Mean ±SD[a]	-0.14 ± 0.15 (7 patients)	-0.06 ± 0.17 (9 patients)	0.01 ± 0.18 (7 patients)
Relative change from baseline VAT/SAT ratio – week 24	Mean ±SD[a]	-15.52 ± 10.68 (7 patients)	-3.8 ± 14.1 (9 patients)	2.2 ± 12.3 (7 patients)
Relative change from baseline VAT/SAT ratio (%) – week 24	LS mean[b] *p<0.05 **p<0.01, versus placebo (ANCOVA)	-17* (7 patients)	-5 (9 patients)	2.0 (5 patients)
Hs-CRP relative change from baseline (%) – week 24	Mean ±SD	-29.8 ± 42.4 (10 patients)	-25.0 ± 50.1 (12 patients)	33.3 ± 72.3 (6 patients)
Hs-CRP relative change from baseline (%) – week 24	LS mean[b] *p<0.05, **p <0.01, versus placebo (ANCOVA)	-48** (10 patients)	-32* (12 patients)	34 (6 patients)

[a]: mean = descriptive mean. LS=Least Square, SD=Standard deviation.

[b]: LS mean = means are computed based on Analysis of Covariance (ANCOVA)

It can be seen from Table 3 that lanifibranor alone or empagliflozin when administered to patients under lanifibranor treatment (empagliflozin plus lanifibranor) induce a redistribution of fat from visceral to subcutaneous fat (VAT/SAT ratio: -17 for empagliflozin plus lanifibranor, -5 for lanifibranor alone and 2 for placebo). Compared to lanifibranor alone, empagliflozin plus lanifibranor leads to a significant decrease in the amount of visceral adipose tissue (-37.91for empagliflozin plus lanifibranor versus

11.03 for lanifibranor alone versus -10.54 for placebo). SGLT2 inhibitor thus allows preventing cardiovascular diseases in patients under treatment with a PPAR agonist, and in particular with lanifibranor.

Example 4: Others effects on SGLT2 inhibitor (empagliflozin) in patients treated with a PPAR agonist (lanifibranor).

1. Materials and methods:

(a) Clinical Laboratory evaluation:

Clinical laboratory tests for hematology, total chemistry panel, and specialized chemistry are performed at each visit (from screening (visit 1) to 24-week treatment (visit 5)). All blood samples will be collected after at least 8 hours fasting and before trial drug administration.

(b) LiverMultiScan®

LiverMultiScan assessments are performed at screening and 24-week treatment with the patient in fasted state (at least 2 hours after food or beverage). The subject's liver will be evaluated using LiverMultiScan® which is a non-invasive and completely painless magnetic resonance imaging (MRI) technology that does not require the use of anesthesia, sedation or contrast injection. The imaging protocol takes only about 10 min, in which parametric maps are taken of the liver, using quantitative imaging. The quantitative images taken by MR based LiverMultiScan® technique will be used to measure hepatic fat content (MRI PDFF), measured by IDEAL (Iterative Decomposition of water and fat with Echo Asymmetry and Least squares estimation) and presented as %; and cT1 that correlates with liver fibrosis and inflammation, derived by an algorithmic correction of T1 (ms) by T2 and presented in ms. An MRI PDFF cut-off of ≥ 5% indicates hepatic steatosis; a cT1 ≥ 800 ms would suggest NASH, and cT1 ≥ 875 ms would indicate a patient has high likelihood of high-risk NASH (NASH with significant fibrosis, F ≥ 2). A 30% relative decline in MRI PDFF predicts a CRN-NASH fibrosis score improvement ≥ 1 stage. MRI PDFF is determined using a 6-echo gradient echo pulse sequence covering the liver in the axial plane. Analysis is performed by semi-automatic contouring of the liver in every slice avoiding major vessels and bile ducts. The method applies multi-peak lipid spectral models and simultaneous quantification and correction for T2. The liver fat value (PDFF) is the mean value of all voxels in the identified volume of interest.

cT1 imaging is an MRI-derived measurement of iron-corrected T1 mapping (cT1). It is a non-invasive, quantitative and accurate biomarker which correlates with ballooning, fibrosis and NAS. The cT1 metric is standardized across all MRI manufacturers. Conditions which increase the extracellular fluid content, such as inflammation and fibrosis, cause a higher cT1, which has been shown to predict clinical outcomes in

patients with chronic liver disease. T1 mapping measures longitudinal relaxation time, which can be used as an indication of regional tissue water content. cT1 is measured by using the modified look-locker inversion (LMS MOLLI) sequence, which is a multi-slice, multi-breath-hold, cardiac-gated acquisition performed at end-expiration. It is determined using a five-slice transverse acquisition with one breath-hold of approximately 10 seconds per slice. This protocol uses a shortened modified look-locker inversion (ShMOLLI) acquisition on GE and Siemens scanners, and a MOLLI acquisition on Philips.

2. Results

The results are presented in Table 4.

Table 4: Additional effects on SGLT2 inhibitor (empagliflozin) in patients treated with a PPAR agonist (lanifibranor).

Treatment groups		Group 1: Empagliflozin plus Lanifibranor	Group 2: Lanifibranor	Group 3: Placebo
HbA1c absolute changes (%) – week 12	Mean ±SD[a]	-1.62 ± 1.11 (11 patients)	-1.16 ± 0.47 (11 patients)	-0.30 ± 0.45 (12 patients)
HbA1c absolute changes (%) – week 24	Mean ±SD[a]	-1.61 ± 0.87 (10 patients)	-1.11 ± 0.44 (11 patients)	-0.11 ± 0.42 (9 patients)
HbA1c absolute changes (%) – week 12	LS mean[b1] *p<0.01 **p<0.001, versus placebo (MMRM)	-1.50** (13 patients)	-1.17* (11 patients)	0.05 (13 patients)
HbA1c absolute changes (%) – week 24		-1.54** (13 patients)	-1.11** (11 patients)	0.16 (13 patients)
Percentage of responders at week 24	HbA1c<6.5%	50% (10 patients)	50% (12 patients)	0% (10 patients)
Percentage of responders at week 24	HbA1c absolute decrease ≥1%	80.0% (10 patients)	58.3% (12 patients)	0% (10 patients)
Liver parameters				
AST absolute changes from baseline (U/L) – week 4	Mean ±SD[a]	-4.8 ± 7.0 (12 patients)	-12.8 ± 18 (12 patients)	1.5 ± 8.4 (13 patients)
AST absolute changes from baseline (U/L)	Mean ±SD[a]	-10.5 ± 24.6 (11 patients)	-16.1 ± 18.3 (12 patients)	4.1 ± 11.2 (13 patients)

– week 12				
AST absolute changes from baseline (U/L) – week 24	Mean ±SD[a]	-21.7 ± 19.7 (9 patients)	-15.3 ± 24.0 (12 patients)	2.1 ± 12.0 (9 patients)
AST relative changes from baseline (U/L) – week 4	LS mean[b1] *p<0.05, **p<0.01, ***p<0.001, versus placebo (MMRM)	-13.79* (13 patients)	-20.99** (12 patients)	0.56 (13 patients)
AST relative changes from baseline (U/L) – week 12		-13.99 (13 patients)	-31.50** (12 patients)	7.02 (13 patients)
AST relative changes from baseline (U/L) – week 24		-38.53 *** (13 patients)	-24.06** (12 patients)	9.78 (13 patients)
ALT absolute changes from baseline (U/L) – week 4	Mean ±SD[a]	-18.4 ± 20.2 (13 patients)	-21.4 ± 22.5 (12 patients)	-1.5 ± 5.8 (13 patients)
ALT absolute changes from baseline (U/L) – week 12	Mean ±SD[a]	-24.5 ± 35 (11 patients)	-30.2 ± 29 (12 patients)	-0.9 ± 7.5 (13 patients)
ALT absolute changes from baseline (U/L) – week 24	Mean ±SD[a]	-28.8 ± 35.3 (12 patients)	-38.1 ± 39.3 (9 patients)	-1.3 ± 15.6 (9 patients)
ALT relative changes from baseline (U/L) – week 4	LS mean[b1] *p<0.05, **p<0.01, ***p<0.001 versus placebo (MMRM)	-26.64* (13 patients)	-26.59* (12 patients)	-4.8 (13 patients)
ALT relative changes from baseline (U/L) – week 12		-34.14** (13 patients)	-44.25*** (12 patients)	-6.75 (13 patients)
ALT relative changes from baseline (U/L) – week 24		-47.79*** (13 patients)	-35.61** (12 patients)	-2.27 (13 patients)
GGT absolute changes from baseline (U/L) – week 4	Mean ±SD[a]	-16.92 ± 16.1 (13 patients)	-16.18 ± 12.5 (11 patients)	2.08 ± 14 (13 patients)
GGT absolute changes from baseline (U/L) – week 12	Mean ±SD[a]	-25.27 ± 18.2 (11 patients)	-17.27 ± 16.4 (11 patients)	7.58 ± 27.2 (12 patients)
GGT absolute changes from baseline (U/L) – week 24	Mean ±SD[a]	-24.40 ± 23.3 (10 patients)	-21.0 ± 16.5 (11 patients)	10.89 ± 41.2 (9 patients)

GGT absolute changes from baseline (U/L) – week 24	LS mean [b1] *p<0.05 versus placebo (MMRM)	-17.8 * (13 patients)	-21.9* (11 patients)	22.8 (13 patients)
Glycaemic control and insulin resistance				
Glucose absolute changes from baseline (mmol/L) – week 4	Mean ±SD[a]	-0.90 ± 3.1 (13 patients)	-1.40 ± 1.48 (11 patients)	-0.13 ±2.8 (12 patients)
Glucose absolute changes from baseline (mmol/L) – week 12	Mean ±SD[a]	-2.55 ± 1.29 (11 patients)	-1.95 ± 1.98 (11 patients)	-0.64 ± 3.35 (12 patients)
Glucose absolute changes from baseline (mmol/L) – week 24	Mean ±SD[a]	-1.96 ± 1.96 (10 patients)	-2.39 ± 1.58 (11 patients)	-0.16 ± 3.29 (9 patients)
Glucose absolute changes from baseline (mmol/L) – week 24	LS mean[b1] *p<0.05 **p<0.01, versus placebo (MMRM)	-1.98 * (13 patients)	-2.36** (11 patients)	-0.23 (13 patients)
Insulin absolute changes from baseline (pmol/L) – week 4	Mean ±SD[a]	-66.8 ± 229.7 (13 patients)	-36.1 ± 64.8 (11 patients)	38.7 ± 160.3 (13 patients)
Insulin absolute changes from baseline (pmol/L) – week 12	Mean ±SD[a]	-95.4 ± 162.9 (11 patients)	-60.6 ± 53.0 (11 patients)	-54.4 ± 161.6 (12 patients)
Insulin absolute changes from baseline (pmol/L) – week 24	Mean ±SD[a]	-136.1 ± 170.9 (10 patients)	-48.5 ± 77.9 (10 patients)	-63.5 ± 200.5 (9 patients)
Insulin absolute changes from baseline (pmol/L) – week 24	LS mean[b1] *p<0.05 versus placebo (MMRM) † p<0.05, versus baseline (MMRM)	-101.8 † (13 patients)	-101.18 † (11 patients)	-57.0 (13 patients)
Insulin relative	LS mean[b1] *p<0.05 versus	-38.16 * (13 patients)	-33.48 (11 patients)	10.17 (13

changes from baseline (%) – week 24	placebo (MMRM) † p<0.05, versus baseline (MMRM)			patients)
HOMA-IR absolute changes from baseline – week 4	Mean ±SD[a]	-0.5 ±28.7 (13 patients)	-2.0 ±3.82 (11 patients)	-0.6±18.2 (12 patients)
HOMA-IR absolute changes from baseline – week 12	Mean ±SD[a]	-9.0 ± 8.65 (11 patients)	-4.6 ± 3.11 (11 patients)	-5.20 ± 20.9 (12 patients)
HOMA-IR absolute changes from baseline – week 24	Mean ±SD[a]	-8.6 ± 12.5 (10 patients)	-3.30 ± 3.39 (10 patients)	-7.30 ± 23.3 (9 patients)
HOMA-IR relative changes from baseline (%) – week 24	LS mean[b1] *p<0.05, **p<0.01 versus placebo (MMRM)	-45.23* (13 patients)	- 50.79** (11 patients)	35.01 (13 patients)
Lipids parameters				
HDL-C absolute changes from baseline (mmol/L) – week 4	Mean ±SD[a]	0.07 ± 0.18 (13 patients)	0.20 ± 0.18 (12 patients)	-0.06 ± 0.09 (13 patients)
HDL-C absolute changes from baseline (mmol/L) – week 12	Mean ±SD[a]	0.17 ± 0.17 (11 patients)	0.19 ± 0.15 (12 patients)	0.01 ± 0.13 (13 patients)
HDL-C absolute changes from baseline (mmol/L) – week 24	Mean ±SD[a]	0.16± 0.30 (10 patients)	0.17 ± 0.17 (12 patients)	0.02 ± 0.12 (9 patients)
HDL-C absolute changes from baseline (mmol/L) – week 24	LS mean[b1] *p<0.05 versus placebo (MMRM) † p<0.05, versus baseline (MMRM)	0.15† (13 patients)	0.17† (12 patients)	0.02 (13 patients)
HDL-C relative changes from baseline (%) – week 24	LS mean[b1] *p<0.05 versus placebo (MMRM) † p<0.05,	15.30† (13 patients)	16.48† (12 patients)	2.55† (13 patients)

	versus baseline (MMRM)			
Triglycerides absolute changes from baseline (mmol/L) – week 24	Mean ±SD[a]	-0.48 ±0.5 (9 patients)	-1.27 ±2.0 (11 patients)	-0.07 ±0.3 (9 patients)
Triglycerides relative changes from baseline (%) – week 24	LS mean[b1] *p<0.01 versus placebo (MMRM)	-26.5* (12 patients)	-25.6* (11 patients)	-2.4 (13 patients)
Adiponectin fold change from baseline – week 24	LS mean[b1] *p<0.01 versus placebo (MMRM)	3.03* (13 patients)	2.87* (11 patients)	1.14 (13 patients)
Liver Fat and markers of inflammation and fibrosis				
Fat liver absolute change from baseline measured by MRI-PDFF (%) – week 24	Mean ±SD[a]	-9.25 ± 8.68 (11 patients)	-9.65 ± 7.27 (12 patients)	-1.01 ± 3.61 (9 patients)
Liver fat relative change from baseline measured by MRI-PDFF (%) – week 24	LS mean[b2] *p<0.05 **p<0.01 versus placebo (ANCOVA)	- 41* (11 patients)	- 49** (12 patients)	-5 (9 patients)
Percentage of responders at week 24	Liver fat Relative reduction of ≥30%	64% (11 patients)	83% (12 patients)	0% (9 patients)
Percentage of responders at week 24	Liver fat Absolute reduction of ≥5%	64% (11 patients)	67% (12 patients)	11% (9 patients)
Inflammation and fibrosis absolute change from baseline measured by cT1 (ms) – week 24	Mean ±SD[a]	-83.36 ± 112 (11 patients)	-87.50 ± 99 (12 patients)	-10.25 ± 66 (8 patients)
Inflammation and fibrosis absolute change from baseline measured by cT1 (ms) – week 24	LS mean[b2] *p<0.2, versus placebo (ANCOVA)	-75 * (11 patients)	-86* (12 patients)	-12 (8 patients)

Percentage of responders at week 24	cT1 Absolute reduction of >80ms	45.5% (11 patients)	50.0% (12 patients)	12.5% (8 patients)
TIMP-1 absolute change from baseline (ug/L) – week 24	Mean ±SD[a]	-29.22±33.5 (11 patients)	-33.72±26.3 (10 patients)	-15.42±47.1 (9 patients)
TIMP-1 absolute change from baseline (ug/L) – week 24	LS mean[b2] *p<0.05, versus placebo (ANCOVA)	-40.0 (11 patients)	-42.8* (10 patients)	-6.8 (9 patients)
P3NP absolute change from baseline (ug/L)– week 24	Mean ±SD[a]	-1.50±3.8 (11 patients)	-1.20±2.6 (10 patients)	0.10±2.7 (9 patients)
P3NP absolute change from baseline (ug/L) – week 24	LS mean[b2] versus placebo (ANCOVA)	-1.44 (11 patients)	-1.22 (10 patients)	0.12 (9 patients)
Pro-C3 absolute change from baseline (ng/mL)– week 24	Mean ±SD[a]	-3.28±14.3 (11 patients)	-0.70±9.2 (12 patients)	6.29±13.8 (9 patients)
Pro-C3 absolute change from baseline (ng/mL) – week 24	LS mean[b2] *p<0.10 (ANCOVA), versus placebo (ProC3 method: ROCHE Cobas e801)	-3.54* (11 patients)	-1.26 (12 patients)	7.33 (9 patients)
Hyaluronic acid absolute change from baseline (ug/L) – week 24	Mean ±SD[a]	45.88±105 (11 patients)	24.54±43 (10 patients)	-8.72±51 (9 patients)
Hyaluronic acid absolute change from baseline (ug/L) – week 24	LS mean[b2] *p<0.1 ** p<0.05, versus placebo (ANCOVA)	67.36 ** (11 patients)	43.10 * (10 patients)	-16.75 (9 patients)
Liver stiffness measurement (LSM) and Controlled attenuation parameter (CAP)				
Liver stiffness absolute change from baseline	Mean ±SD[a]	-61 ± 51 (10 patients)	-17 ± 50 (11 patients)	-25 ± 59 (13 patients)

measured by CAP (dB/m) – week 12				
Liver stiffness absolute change from baseline measured by CAP (dB/m) – week 24	Mean ±SD[a]	-79 ± 46 (9 patients)	-26 ± 44 (12 patients)	-6 ± 46 (9 patients)
Liver stiffness absolute change from baseline measured by LMS (kPa) – week 12	Mean ±SD[a]	0.91 ± 3.2 (11 patients)	-0.13 ± 3.4 (11 patients)	1.17 ± 3.1 (13 patients)
Liver stiffness absolute change from baseline measured by LMS (kPa) – week 24	Mean ±SD[a]	-1.34 ± 1.2 (10 patients)	-1.76 ± 2.5 (12 patients)	2.73 ± 7.7 (9 patients)
Others parameters				
Spleen volume absolute change from baseline (cm3) – week 24	Mean ±SD[a]	-0 ± 50 (10 patients)	-15 ± 16 (11 patients)	8 ± 19 (9 patients)
Spleen volume relative change from baseline (%) – week 24	LS mean[b2] *p<0.05, versus placebo (ANCOVA)	-1.3 (10 patients)	-8.8* (11 patients)	3.0 (9 patients)
Liver volume absolute change from baseline (cm3) – week 24	Mean ±SD[a]	-256 ± 287 (8 patients)	-144 ± 266 (9 patients)	-29 ± 136 (9 patients)
Liver volume relative change from baseline (%) – week 24	LS mean[b2] *p<0.1, versus placebo (ANCOVA)	-10.1* (8 patients)	-7.1 (9 patients)	-0.4 (9 patients)

[a]: mean = descriptive mean. LS=Least Square. SD=Standard deviation.

[b1]: LS mean = means are computed based on Mixed Model Repeated Measure (MMRM) linear model

[b2]: LS mean = means are computed based on Analysis of Covariance (ANCOVA)

Like lanifibranor, empagliflozin when administered to patients under lanifibranor treatment improves HbA1c. Like lanifibranor, empagliflozin when administered to patients under lanifibranor treatment improves markers of liver injury (see ALT, AST). Empagliflozin when administered to patients under lanifibranor treatment improves insulin sensitivity (see Insulin and HOMA-IR). Like lanifibranor, empagliflozin when administered to patients under lanifibranor treatment improves markers of inflammation and fibrosis measured by cT1. Significant improvements of hepatic steatosis and composite MASH activity and fibrosis were observed when empagliflozin is administered to patients under lanifibranor treatment, with a mean relative MRI-PDFF change of -49% and a mean absolute cT1 changes of -75ms.

Liver tests (ALT, AST, GGT), fibrosis markers (TIMP-1, P3NP, Pro-C3), insulin, HOMA-IR, hs-CRP, ferritin, glycemia, lipid profile (HDL-C, Triglycerides) are improved when empagliflozin is administered to patients under lanifibranor treatment and adiponectin is increased by a mean of 3-fold when empagliflozin is administered to patients under lanifibranor treatment.

Like lanifibranor, empagliflozin when administered to patients under lanifibranor treatment improves HDL-C. Like lanifibranor, empagliflozin when administered to patients under lanifibranor treatment improves markers of cardiometabolic health (see HDL-C, Insulin, HOMA-IR, adiponectin, VAT/SAT ratio), including hepatic steatosis. Like lanifibranor, empagliflozin when administered to patients under lanifibranor treatment contributes to a decrease of spleen volume.

Conclusions:

Empagliflozin when administered to patients under lanifibranor treatment maintains and, in some parameters, improves the therapeutic efficacy of lanifibranor. Empagliflozin when administered to patients under lanifibranor treatment prevents the weight gain and the reduction of hemoglobin induced by lanifibranor treatment.

Empagliflozin when administered to patients under lanifibranor treatment improve noninvasive hepatic and cardiometabolic markers of MASH, including a shift toward SAT, without observed weight gain.

Empagliflozin when administered to patients under lanifibranor treatment prevents or delaying clinical complications of blood disorders, and in particular prevents or delaying the risk of anaemia in a patient having been treated, treated or planned to be treated with lanifibranor.

CLAIMS

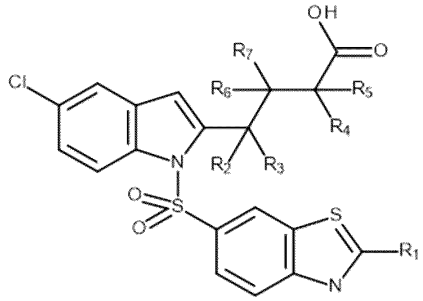
1. Sodium glucose transporter 2 (SGLT2) inhibitor for use for preventing or delaying anaemia or clinical complications of blood disorders in a patient having been treated, treated or planned to be treated with a PPAR agonist.

2. The SGLT2 inhibitor for use of claim 1, wherein the SGLT2 inhibitor is selected from the group consisting of canaglifozin, dapagliflozin, remoglifozin, sergliflozin, empagliflozin, ipragliflozin, tofogliflozin, luseogliflozin, sotagliflozin, ertuglifozin, bexagliflozin, henagliflozin, janagliflozin, tianagliflozin, and pharmaceutically acceptable salts thereof.

3. The SGLT2 inhibitor for use of any one of claims 1 to 2, wherein the SGLT2 inhibitor is empagliflozin.

4. The SGLT2 inhibitor for use of any one of claims 1 to 3, wherein the PPAR agonist is selected from the group consisting of lanifibranor, a deuterated form of lanifibranor and pharmaceutically acceptable salts thereof.

5. The SGLT2 inhibitor for use of claim 4, 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, preferably 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.

6. The SGLT2 inhibitor for use of any one of claims 1 to 5, wherein the patient is diagnosed with a liver disease.

7. The SGLT2 inhibitor for use of claim 6, wherein the liver disease is selected from liver fibrosis, liver steatosis, fatty liver disease, acute decompensation, 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, diabetes, autoimmune cholangitis, primary biliary cholangitis, primary sclerosing cholangitis, autoimmune cholangiopathy, hepatocarcinoma and a combination of these diseases.

8. The SGLT2 inhibitor for use of any one of claims 1 to 7, wherein blood disorders or clinical complications of blood disorders are a reduction in the amount of at least one biomarker compared to the reference amount of said at least one biomarker, wherein said at least one biomarker is selected from: hemoglobin, ferritin, haptoglobin, hematocrit, transferrin, vitamin B12 and a combination thereof.

9. The SGLT2 inhibitor for use of claim 8, wherein the reduction in the amount of at least one biomarker is equal or greater than 5% compared to the reference amount of at least one biomarker of said patient.

10. The SGLT2 inhibitor for use of any one of claims 1 to 9, wherein the patient:

a. is diagnosed with one or more of the conditions selected from the group consisting of overweight, obesity, visceral obesity and abdominal obesity; or

b. displays at least one of the following conditions before treatment with a PPAR agonist:

(a) being over the age of 40 years;

(b) a poor iron absorption;

(c) a body mass index equal to or greater than 30 kg/m2;

(d) a reference amount of HbA1c equal to or greater than 7.0 %;

(e) a reference amount of hemoglobin equal to or below than 140 g/L;

(f) diagnosed with one of the following diseases: diabetes, dyslipidemia, cardiovascular diseases, cancer, polycystic ovary syndrome, acute lung injury, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, insulin resistance, obesity, diseases linked to endothelial dysfunction, atherosclerosis, myocardial infarction, hypertension, cerebrovascular problems, inflammatory diseases such as rheumatoid arthritis, chronic kidney disease, a pulmonary fibrotic disorder such as idiopathic

pulmonary fibrosis, systemic sclerosis and neurodegeneration such as Alzheimer's disease or Parkinson's disease;

(g) diagnosed with a liver disease;

(h) diagnosed with non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, metabolic-associated fatty liver disease, metabolic-associated steatohepatitis and/or diabetes.

11. The SGLT2 inhibitor for use of any one of claims 1 to 10, wherein the patient further displays at least one of the following conditions before treatment with a PPAR agonist:

a. aspartate aminotransferase (AST) amount greater than or equal to 10 U/L;

b. alanine aminotransferase (ALT) amount greater than or equal to 10 U/L;

c. gamma glutamyl transferase (GGT) amount greater than or equal to 3 U/L;

d. fasting blood glucose amount greater than or equal to 4 mmol/L;

e. HDL-cholesterol blood amount below than or equal to 2.50 mmol/L;

f. triglyceride blood amount greater than or equal to 0.70 mmol/L;

g. ferritin amount greater than or equal to 6 µg/L;

h. a systolic blood pressure greater than or equal to 95 mm Hg and a diastolic blood pressure greater than or equal to 60 mm Hg;

i. ratio visceral adipose tissue (VAT)/ subcutaneous adipose tissue (SAT) (VAT/SAT) greater than or equal to 0.30;

j. cT1 amount greater than or equal to 700 ms.

12. The SGLT2 inhibitor for use of any one of claims 1 to 11, wherein said prevention comprises the administration in combination or alternation or sequentially of the PPAR agonist and the SGLT2 inhibitor.

13. The SGLT2 inhibitor for use of any one of claims 1 to 12, wherein the patient is treated or is planned to be treated with a PPAR agonist and wherein the first dose of SGLT2 inhibitor is:

(a) administered at least one day after the start of the treatment with the PPAR agonist; or

(b) administered at the same time as the first dose of the treatment with the PPAR agonist; or

(c) administered at least one day before the start of the treatment with the PPAR agonist.

14. The SGLT2 inhibitor for use of any one of claims 1 to 13, wherein said SGLT2 inhibitor is empagliflozin or a pharmaceutically acceptable salt thereof, and said PPAR agonist is selected from the group comprising lanifibranor, a deuterated form of lanifibranor and pharmaceutically acceptable salts thereof.

15. A method for preventing or delaying clinical complications of blood disorders, in a patient having been treated, treated or planned to be treated with a PPAR agonist, the method comprising administering to the patient a suitable dosage of a SGLT2 inhibitor.

16. The method of claim 15, wherein the SGLT2 inhibitor and the PPAR agonist are administered in combination or alternation or sequentially to the patient.

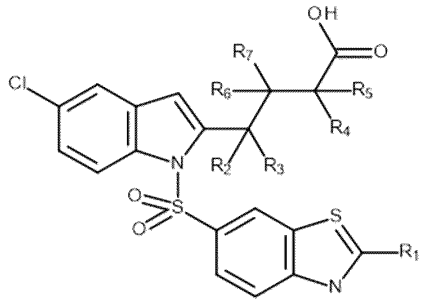
17. The method of any one of claims 15 to 16, wherein the patient is treated or is planned to be treated with a PPAR agonist and wherein a first dose of SGLT2 inhibitor is:
(a) administered at least one day after the start of the treatment with the PPAR agonist; or
(b) administered at the same time as the first dose of the treatment with the PPAR agonist; or
(c) administered at least one day before the start of the treatment with the PPAR agonist.

18. The method of any one of claims 15 to 17, wherein the SGLT2 inhibitor is selected from the group consisting of canaglifozin, dapagliflozin, remoglifozin, sergliflozin, empagliflozin, ipragliflozin, tofogliflozin, luseogliflozin, sotagliflozin, ertuglifozin, bexagliflozin, henagliflozin, janagliflozin, tianagliflozin, and pharmaceutically acceptable salts thereof.

19. The method of claim 18, wherein the SGLT2 inhibitor is empagliflozin.

20. The method of any one of claims 15 to 19, wherein the PPAR agonist is selected from the group consisting of lanifibranor, a deuterated form of lanifibranor and pharmaceutically acceptable salts thereof.

21. The method of claim 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, preferably 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.

22. A method for preventing a reduction in hemoglobin levels in a patient having been treated, treated or planned to be treated with a PPAR agonist, comprising administering to the patient a suitable dosage of SGLT2 inhibitor.

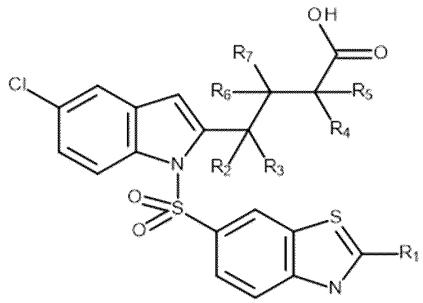
23. A method for reducing or preventing the discontinuation of a treatment with a PPAR agonist in a patient treated with such PPAR agonist, the method comprising administering to the patient a suitable dosage of a SGLT2 inhibitor.

24. The method of any one of claims 22 to 23, wherein the SGLT2 inhibitor is selected from the group consisting of canaglifozin, dapagliflozin, remoglifozin, sergliflozin, empagliflozin, ipragliflozin, tofogliflozin, luseogliflozin, sotagliflozin, ertuglifozin, bexagliflozin, henagliflozin, janagliflozin, tianagliflozin, and pharmaceutically acceptable salts thereof.

25. The method of claim 24, wherein the SGLT2 inhibitor is empagliflozin.

26. The method of any one of claims 22 to 25, wherein the PPAR agonist is selected from the group consisting of lanifibranor, a deuterated form of lanifibranor and pharmaceutically acceptable salts thereof.

27. The method of claim 26, 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, preferably 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.