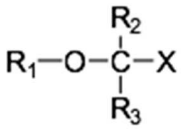
Claims

1. ~~A~~Use of ~~combination therapy comprising~~ a ~~first~~ compound of Formula (II)



(II)

wherein R_1 is selected from a C_{10}-C_{22} alkenyl having 3-6 double bonds;

R_2 and R_3 are the same or different and are selected from the group of a hydrogen atom, a hydroxy group, an alkyl group, a halogen atom, an alkoxy group, an acyloxy group, an acyl group, an alkenyl group, an alkynyl group, an aryl group, an alkylthio group, an alkoxycarbonyl group, a carboxy group, an alkylsulfinyl group, an alkylsulfonyl group, an amino group, and an alkylamino group; wherein R_2 and R_3 can be connected in order to form a cycloalkane like cyclopropane, cyclobutane, cyclopentane, or cyclohexane;

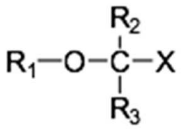
X is a carboxylic acid or a derivative thereof, ~~;~~ wherein the derivative is a carboxylate, such as a carboxylic ester; a glyceride; an anhydride; a carboxamide; a phospholipid; or a hydroxymethyl; or a prodrug thereof;

or a pharmaceutically acceptable salt, solvate, or solvate of such a salt thereof,

~~and at least one additional active agent chosen from a glucagon-like peptide 1 (GLP-1) receptor agonist, an acetyl-CoA carboxylase (ACC) inhibitor, and a farnesoid X receptor (FXR) agonist,~~

in the manufacture of a medicament for ~~use in~~the therapeutic and/or prophylactic treatment of non-alcoholic steatohepatitis (NASH), wherein the medicament is co-administered with at least one additional active agent chosen from a glucagon-like peptide 1 (GLP-1) receptor agonist, an acetyl-CoA carboxylase (ACC) inhibitor, and a farnesoid X receptor (FXR) agonist.

2. Use of a compound of Formula (II)



(II)

wherein R_1 is selected from a C_{10}-C_{22} alkenyl having 3-6 double bonds;

R_2 and R_3 are the same or different and are selected from the group of a hydrogen atom, a hydroxy group, an alkyl group, a halogen atom, an alkoxy group, an acyloxy group, an acyl group, an alkenyl group, an alkynyl group, an aryl group, an alkylthio group, an alkoxycarbonyl

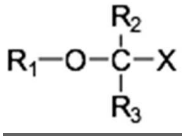
group, a carboxy group, an alkylsulfinyl group, an alkylsulfonyl group, an amino group, and an alkylamino group; wherein R_2 and R_3 can be connected in order to form a cycloalkane like cyclopropane, cyclobutane, cyclopentane, or cyclohexane;

X is a carboxylic acid or a derivative thereof, wherein the derivative is a carboxylate, such as a carboxylic ester; a glyceride; an anhydride; a carboxamide; a phospholipid; or a hydroxymethyl; or a prodrug thereof;

or a pharmaceutically acceptable salt, solvate, or solvate of such a salt thereof,

in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of alcoholic steatohepatitis (ASH), wherein the medicament is co-administered with at least one additional active agent chosen from a glucagon-like peptide 1 (GLP-1) receptor agonist, an acetyl-CoA carboxylase (ACC) inhibitor, and a farnesoid X receptor (FXR) agonist.

3. Use of a compound of Formula (II)



(II)

wherein R_1 is selected from a C_{10}-C_{22} alkenyl having 3-6 double bonds;

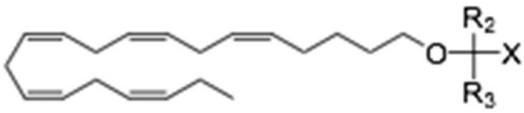
R_2 and R_3 are the same or different and are selected from the group of a hydrogen atom, a hydroxy group, an alkyl group, a halogen atom, an alkoxy group, an acyloxy group, an acyl group, an alkenyl group, an alkynyl group, an aryl group, an alkylthio group, an alkoxycarbonyl group, a carboxy group, an alkylsulfinyl group, an alkylsulfonyl group, an amino group, and an alkylamino group; wherein R_2 and R_3 can be connected in order to form a cycloalkane like cyclopropane, cyclobutane, cyclopentane, or cyclohexane;

X is a carboxylic acid or a derivative thereof, wherein the derivative is a carboxylate, such as a carboxylic ester; a glyceride; an anhydride; a carboxamide; a phospholipid; or a hydroxymethyl; or a prodrug thereof;

or a pharmaceutically acceptable salt, solvate, or solvate of such a salt thereof,

in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of fatty liver disease, wherein the medicament is co-administered with at least one additional active agent chosen from a glucagon-like peptide 1 (GLP-1) receptor agonist, an acetyl-CoA carboxylase (ACC) inhibitor, and a farnesoid X receptor (FXR) agonist.

~~24~~. ~~A combination therapy according to claim 1 for use according to claim 1~~The use of any one of claims 1 to 3, wherein the ~~first~~ compound is of Formula (I), and R_2, R_3, and X are as defined for Formula (II)



(I).

~~35~~. ~~A combination therapy according to claim 1 or 2 for use according to claim 1~~The use according to any one of claims 1 to 4,

wherein ~~for the first compound~~ R_2 and R_3 are independently chosen from a hydrogen atom or linear, branched, and/or cyclic C_1-C_6 alkyl groups;

X is a carboxylic acid or a derivative thereof,~~;~~ wherein the derivative is a carboxylate, such as a carboxylic ester; a glyceride; an anhydride; a carboxamide; a phospholipid; or a hydroxymethyl; or a prodrug thereof;

or a pharmaceutically acceptable salt, solvate, or solvate of such salt thereof~~,~~ ~~for use in treating non-alcoholic steatohepatitis~~.

~~46~~. The ~~combination therapy according to any one of claims 1 to 3 for~~ use ~~according to~~of any one of claims 1 to 5, wherein ~~for the first compound~~ R_2 and R_3 are independently chosen from a hydrogen atom, a methyl group, an ethyl group, a n-propyl group, and an isopropyl group.

~~57~~. The ~~combination therapy according to~~use of any one of claims 1 to ~~35 for use according to claim 1~~, wherein ~~for the first compound~~ R_2 and R_3 are both independently C_1-C_6 alkyl groups.

~~68~~. The ~~combination therapy according to~~use of any one of claims 1 to ~~46 for use according to claim 1~~, wherein ~~for the first compound~~ one of R_2 and R_3 is a hydrogen atom and the other is an ethyl group.

~~79~~. The ~~combination therapy according to~~use of any one of claims 1 to ~~68 for use according to claim 1~~, wherein ~~for the first compound~~ X is a carboxylic acid.

~~8~~10. The ~~combination therapy according to~~use of any one of claims 1 to ~~6~~8 ~~for use according to claim 1~~, wherein ~~for the first compound~~ X is a C_1-C_6 alkyl ester.

~~9~~11. The ~~combination therapy according to~~use of claim 10~~8 for use according to claim 1~~, wherein ~~for the first compound~~ X is chosen from a methyl ester, an ethyl ester, an isopropyl ester, a *n*-butyl ester, and a *tert*-butyl ester.

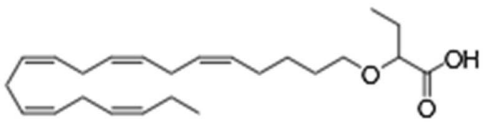
~~10~~12. The ~~combination therapy according to~~use of any one of claims 1 to 3, ~~8~~10, or ~~9~~11 ~~for use according to claim 1~~, wherein ~~for the first compound~~ X is selected from the group of a methyl ester and an ethyl ester.

~~11~~13. The ~~combination therapy according to~~use of any one of claims 1 to ~~6~~8 ~~for use according to claim 1~~, wherein ~~for the first compound~~ X is a glyceride chosen from a triglyceride, a 1,2-diglyceride, a 1,3-diglyceride, a 1-monoglyceride, and a 2-monoglyceride.

~~12~~14. The ~~combination therapy according to~~use of any one of claims 1 to ~~11~~13 ~~for use according to claim 1~~, wherein the ~~first~~ compound is present in the form of an enantiomer, a diastereomer, or a mixture thereof.

~~13~~15. The ~~combination therapy according to~~use of claim 14~~12 for use according to claim 1~~, wherein the first compound is present in its R form, in its S form, or in racemic form.

~~14~~16. The ~~combination therapy according to~~use of any one of claims 1 to 4~~or 2 for use according to claim 1~~, wherein the first compound is 2-(((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-yl)oxy)butanoic acid (Compound A), or a pharmaceutically acceptable salt or ester thereof, and the formula is



(Compound A).

~~15~~17. The ~~combination therapy according to~~use of any one of claims 1 to ~~14~~16 ~~for use according to claim 1~~, wherein the ~~first~~ compound is administered in a dose of between about 5 mg to about 4 g per dose.

~~16~~18. The ~~combination therapy according to~~use of any one of claims 1 to ~~15~~17 ~~for use according to claim 1~~, wherein the ~~first~~ compound is administered once daily.

~~17~~19. The ~~combination therapy according to~~ use of any one of ~~the preceding claims for use according to claim 1~~claims 1 to 18, wherein the additional active agent is chosen from semaglutide, firsocostat, and obeticholic acid (OCA).

~~18~~20. The ~~combination therapy according to~~use of any one of ~~the preceding~~ claims 1 to 19 ~~for use according to claim 1~~, wherein the additional active agent is semaglutide.

~~19~~21. The ~~combination therapy according to~~use of any one of ~~the preceding~~ claims 1 to 20 ~~for use according to claim 1~~, wherein the additional active agent is firsocostat.

~~20~~22. The ~~combination therapy according to~~use of any one of ~~the preceding~~ claims 1 or 4 to 21, wherein the use treats or reverses NASH.

~~21~~23. The ~~combination therapy according to~~use of any one of ~~the preceding~~ claims 1 or 4 to 22, wherein

a) the use reduces the development of hepatic fibrosis or reduces existing hepatic fibrosis in a subject with NASH;

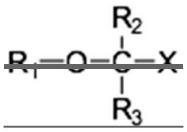
b) the use reduces the development of hepatic inflammation or reduces existing hepatic inflammation in a subject with NASH; and/or

c) the use reduces the development of steatohepatitis or reduces existing steatohepatitis in a subject with NASH.

~~22. The combination therapy according to any one of the preceding claims wherein the use reduces the development of hepatic inflammation or reduces existing hepatic inflammation in a subject with NASH.~~

~~23. The combination therapy according to any one of the preceding claims wherein the use reduces the development of steatohepatitis or reduces existing steatohepatitis in a subject with NASH.~~

24. A combination therapy comprising a first compound of Formula (II)



(II)

wherein R_1 is selected from a C_{10}-C_{22} alkenyl having 3-6 double bonds;

R_2 and R_3 are the same or different and are selected from the group of a hydrogen atom, a hydroxy group, an alkyl group, a halogen atom, an alkoxy group, an acyloxy group, an acyl group, an alkenyl group, an alkynyl group, an aryl group, an alkylthio group, an alkoxycarbonyl group, a carboxy group, an alkylsulfinyl group, an alkylsulfonyl group, an amino group, and an alkylamino group; wherein R_2 and R_3 can be connected in order to form a cycloalkane like cyclopropane, cyclobutane, cyclopentane or cyclohexane;

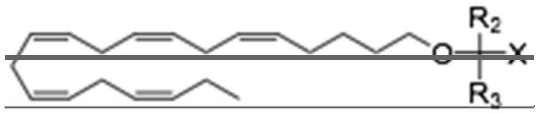
X is a carboxylic acid or a derivative thereof; wherein the derivative is a carboxylate, such as a carboxylic ester; a glyceride; an anhydride; a carboxamide; a phospholipid; or a hydroxymethyl; or a prodrug thereof;

or a pharmaceutically acceptable salt, solvate, or solvate of such a salt thereof,

and at least one additional active agent chosen from a glucagon-like peptide 1 (GLP-1) receptor agonist, an acetyl-CoA carboxylase (ACC) inhibitor, and a farnesoid X receptor (FXR) agonist,

for use in therapeutic and/or prophylactic treatment of alcoholic steatohepatitis (ASH).

25. A combination therapy according to claim 24 for use according to claim 24 wherein the first compound is of Formula (I), and R2, R3, and X are as defined for Formula (II)



(I).

26. A combination therapy according to claim 24 or 25 for use according to claim 24

wherein for the first compound R_2 and R_3 are independently chosen from a hydrogen atom or linear, branched, and/or cyclic C_1-C_6 alkyl groups;

X is a carboxylic acid or a derivative thereof; wherein the derivative is a carboxylate, such as a carboxylic ester; a glyceride; an anhydride; a carboxamide; a phospholipid; or a hydroxymethyl; or a prodrug thereof;

or a pharmaceutically acceptable salt, solvate, or solvate of such salt thereof,

for use in treating non-alcoholic steatohepatitis.

27. The combination therapy according to any one of claims 24 to 26 for use according to claim 24, wherein for the first compound R_2 and R_3 are independently chosen from a hydrogen atom, a methyl group, an ethyl group, a n-propyl group, and an isopropyl group.

28. The combination therapy according to any one of claims 24 to 26 for use according to claim 24, wherein for the first compound R_2 and R_3 are both independently C_1-C_6 alkyl groups.

29. The combination therapy according to any one of claims 24 to 27 for use according to claim 24, wherein for the first compound one of R_2 and R_3 is a hydrogen atom and the other is an ethyl group.

30. The combination therapy according to any one of claims 24 to 29 for use according to claim 24, wherein for the first compound X is a carboxylic acid.

31. The combination therapy according to any one of claims 24 to 29 for use according to claim 24, wherein for the first compound X is a C_1-C_6 alkyl ester.

32. The combination therapy according to claim 31 for use according to claim 24, wherein for the first compound X is chosen from a methyl ester, an ethyl ester, an isopropyl ester, a *n*-butyl ester, and a *tert*-butyl ester.

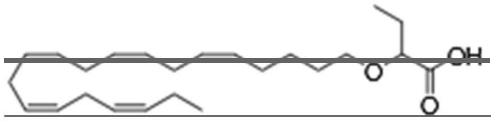
33. The combination therapy according to any one of claims 24, 31 and 32 for use according to claim 24, wherein for the first compound X is selected from the group of a methyl ester and an ethyl ester.

34. The combination therapy according to any one of claims 24 to 29 for use according to claim 24, wherein for the first compound X is a glyceride chosen from a triglyceride, a 1,2-diglyceride, a 1,3-diglyceride, a 1-monoglyceride, and 2-monoglyceride.

35. The combination therapy according to any one of claims 24 to 34 for use according to claim 24, wherein the first compound is present in the form of an enantiomer, diastereomer, or mixture thereof.

~~36. The combination therapy according to claim 35 for use according to claim 24, wherein the first compound is present in its R form, in its S form or in racemic form.~~

~~37. The combination therapy according to claim 24 or 25 for use according to claim 24, wherein the first compound is 2-(((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-yl)oxy)butanoic acid (Compound A), or a pharmaceutically acceptable salt or ester thereof, and the formula is~~



~~(Compound A).~~

~~38. The combination therapy according to any one of claims 24 to 37 for use according to claim 24, wherein the first compound is administered in a dose of between about 5 mg to about 4 g per dose.~~

~~39. The combination therapy according to any one of claims 24 to 38 for use according to claim 24, wherein the first compound is administered once daily.~~

~~40. The combination therapy according to any one of the preceding claims for use according to claim 24, wherein the additional active agent is chosen from semaglutide, firsocostat, and obeticholic acid (OCA).~~

~~41. The combination therapy according to any one of the preceding claims for use according to claim 24, wherein the additional active agent is semaglutide.~~

~~42. The combination therapy according to any one of the preceding claims for use according to claim 24, wherein the additional active agent is firsocostat.~~

~~43~~24. The ~~combination therapy according to~~use of any one of claims ~~24~~2 or 4 to ~~42~~21, wherein the use treats or reverses ASH.

4425. The combination therapy according touse of any one of claims 242, 4 to 4321, or 24, wherein

a) the use reduces the development of hepatic fibrosis or reduces existing hepatic fibrosis in a subject with ASH;

b) the use reduces the development of hepatic inflammation or reduces existing hepatic inflammation in a subject with ASH; and/or

c) the use reduces the development of steatohepatitis or reduces existing steatohepatitis in a subject with ASH.

45. The combination therapy according to any one of claims 24 to 44 wherein the use reduces the development of hepatic inflammation or reduces existing hepatic inflammation in a subject with ASH.

46. The combination therapy according to any one of claims 24 to 45 wherein the use reduces the development of steatohepatitis or reduces existing steatohepatitis in a subject with ASH.

26. The use of any one of claims 3 to 21, wherein the use treats or reverses fatty liver disease.

27. The use of any one of claims 3 to 21 or 26, wherein the use reduces or reverses steatosis.

28. The use of any one of claims 3 to 21, 26, or 27, wherein the fatty liver disease is

a) non-alcoholic fatty liver disease (NAFLD); or

b) alcoholic fatty liver disease (ALD).

29. The use of any one of claims 3 to 21 or 26 to 28, wherein the fatty liver disease is not accompanied by an inflammatory response and cellular damage.

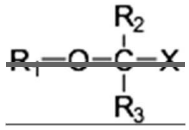
4730. A combination therapy according toThe use of any one of the preceding claims 1 to 29 for use according to claim 1 or 24, wherein the first compound is formulated in a composition.

4831. A combination therapy according toThe use of claim 4730, for use according to claim 1, wherein the composition is formulated for oral administration.

4932. The combination therapy according to any one use of claims 47 to 48 for use according to claim 1 or 2430 or claim 31, wherein the pharmaceutical composition further comprises at least one binder, excipient, diluent, or antioxidant, or any combinations thereof.

50. The composition according to any one of claims 47 to 49 for use according to claim 1 or 24, wherein the compound is 2-(((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-yl)oxy)butanoic acid.

51. A method of treating non-alcoholic steatohepatitis (NASH) and/or alcoholic steatohepatitis (ASH) in a subject in need thereof, comprising administering to the subject a pharmaceutically effective amount of a first compound of formula (II):



(II)

wherein R_1 is selected from a C_{10}-C_{22} alkenyl having 3-6 double bonds; R_2 and R_3 are the same or different and are selected from the group of a hydrogen atom, a hydroxy group, an alkyl group, a halogen atom, an alkoxy group, an acyloxy group, an acyl group, an alkenyl group, an alkynyl group, an aryl group, an alkylthio group, an alkoxycarbonyl group, a carboxy group, an alkylsulfinyl group, an alkylsulfonyl group, an amino group, and an alkylamino group; wherein R_2 and R_3 can be connected in order to form a cycloalkane like cyclopropane, cyclobutane, cyclopentane or cyclohexane;

X is a carboxylic acid or a derivative thereof; wherein the derivative is a carboxylate, such as a carboxylic ester; a glyceride; an anhydride; a carboxamide; a phospholipid; or a hydroxymethyl; or a prodrug thereof;

or a pharmaceutically acceptable salt, solvate, or solvate of such a salt, thereof; and a pharmaceutically effective amount of at least one additional active agent chosen from a glucagon-like peptide 1 (GLP-1) receptor agonist, an acetyl-CoA carboxylase (ACC) inhibitor, and a farnesoid X receptor (FXR) agonist.

52. The method according to claim 51, wherein the first compound is of Formula (I):



(II).

53. The method according to claim 51 or 52,

wherein for the first compound R_2 and R_3 are independently chosen from a hydrogen atom or linear, branched, and/or cyclic C_1-C_6 alkyl groups; and

X is a carboxylic acid or a derivative thereof; wherein the derivative is a carboxylate, such as a carboxylic ester; a glyceride; an anhydride; a carboxamide; a phospholipid; or a hydroxymethyl; or a prodrug thereof;

or a pharmaceutically acceptable salt, solvate, or solvate of such a salt, thereof.

54. The method according to any one of claims 51 to 53, wherein for the first compound R_2 and R_3 are independently chosen from a hydrogen atom, a methyl group, an ethyl group, an n-propyl group, and an isopropyl group.

55. The method according to any one of claims 51 to 54, wherein for the first compound R_2 and R_3 are both independently C_1-C_6 alkyl groups.

56. The method according to any one of claims 51 to 55, wherein for the first compound one of R_2 and R_3 is a hydrogen atom and the other is an ethyl group.

57. The method according to any one of claims 51 to 56, wherein for the first compound X is a carboxylic acid.

58. The method according to any one of claims 51 to 56, wherein for the first compound X is a C_1-C_6 alkyl ester.

59. The method according to claim 51, wherein for the first compound X is chosen from a methyl ester, an ethyl ester, an isopropyl ester, a *n*-butyl ester, and a *tert*-butyl ester.

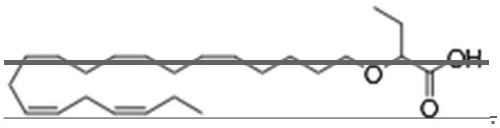
60. The method according to any one of claims 51, 58, or 59 wherein for the first compound X is chosen from a methyl ester and an ethyl ester.

61. The method according to any one of claims 51 to 56, wherein for the first compound X is a glyceride chosen from a triglyceride, a 1,2-diglyceride, a 1,3-diglyceride, a 1-monoglyceride, and 2-monoglyceride.

62. The method according to any one of claims 51 to 61, wherein the first compound is present in the form of an enantiomer, diastereomer, or mixture thereof.

63. The method according to claim 62, wherein the first compound is present in its R form, in its S form, or in racemic form.

64. The method according to claim 51, wherein the first compound is 2-(((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-yl)oxy)butanoic acid (Compound A), or a pharmaceutically acceptable salt or ester thereof, and the formula is



65. The method according to any one of claims 51 to 64, wherein said compound is administered in a dose of between about 5 mg to about 4 g per dose.

66. The method according to any one of claims 51 to 65, wherein the compound is administered once daily.

67. The method according to any one of claims 51 to 66, wherein the additional active agent is chosen from semaglutide, firsocostat, and obeticholic acid (OCA).

68. The method according to any of claims 51 to 67, wherein the additional active agent is semaglutide.

69. The method according to any one of claims 51 to 67, wherein the additional active agent is firsocostat.

70. The method according to any one of claims 51 to 69, wherein the method treats or reverses NASH and/or ASH.

71. The method according to any one of claims 51 to 70, wherein the method comprises prophylactically treating NASH and/or ASH.

72. The method according to any one of claims 51 to 71, wherein the method reduces or prophylactically treats the development of hepatic fibrosis or reduces existing hepatic fibrosis.

73. The method according to any one of claims 51 to 72, wherein the use reduces the development of steatohepatitis or reduces existing steatohepatitis.

74. The method according to any one of claims 51 to 73, wherein the first compound is formulated as a pharmaceutical composition.

75. The method according to claim 74, wherein the pharmaceutical composition is formulated for oral administration.

76. The method according to claim 74 or 75, wherein the pharmaceutical composition further comprises at least one binder, excipient, diluent, or antioxidant, or any combination thereof.

77. The method according to any one of claims 51 to 76, wherein the first compound is 2-(((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-yl)oxy)butanoic acid.

78. The method according to any one of claims 51 to 77, wherein the method of treatment is prophylactic.

~~79. The method according to any one of claims 51 to 78, wherein the first compound and at least one additional active agent are co-administered by simultaneous administration, sequential administration, overlapping administration, interval administration, continuous administration, or a combination thereof.~~

~~80. The method according to any one of claims 51 to 79, further comprising co-administering at least one further additional active agent.~~

~~81~~33. The ~~combination therapies and methods according to~~use of any one of ~~the preceding~~ claims 1 to 32, wherein the ~~first~~ compound is administered at a dosage of about 600 mg daily.

~~82~~34. The ~~combination therapies and methods according to~~use of any one of ~~the preceding~~ claims 1 to 32, wherein the compound is administered at a dosage of about 300 mg daily.

~~83~~35. The ~~combination therapies and methods according to~~use of any one of ~~the preceding~~ claims 1, 2, 4 to 25, or 30 to 34, wherein

a) hepatic inflammatory cells are reduced by 30-50% or by 60-80%;

b) the liver hydroxyproline content is decreased by 20-40%; and/or

c) the hepatic fibrotic area as determined by picrosirius red staining is decreased by 30-50%.

~~84. The combination therapies and methods according to any one of the preceding claims, wherein hepatic inflammatory cells are reduced by 60-80%.~~

~~85~~36. The ~~combination therapies and methods according to~~ use of any one of ~~the preceding~~ claims 1 to 35, wherein

a) hepatic steatosis area is reduced by 70-90%;

b) the percentage of hepatocytes with lipid droplets is reduced by 70-90%;

c) the NAFLD activity (NAS) score is reduced; and/or

d) the steatosis score is reduced.

~~86. The combination therapies and methods according to any one of the preceding claims, wherein the percentage of hepatocytes with lipid droplets is reduced by 70-90%.~~

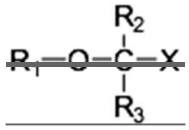
87. The combination therapies and methods according to any one of the preceding claims, wherein the NAFLD activity (NAS) score is reduced.

88. The combination therapies and methods according to any one of the preceding claims, wherein the steatosis score is reduced.

89. The combination therapies and methods according to any one of the preceding claims, wherein the liver hydroxyproline content is decreased by 20-40%.

90. The combination therapies and methods according to any one of the preceding claims, wherein the hepatic fibrotic area as determined by picrosirius red staining is decreased by 30-50%.

91. A combination therapy comprising a first compound of Formula (II)



(II)

wherein R_1 is selected from a C_{10}-C_{22} alkenyl having 3-6 double bonds;

R_2 and R_3 are the same or different and are selected from the group of a hydrogen atom, a hydroxy group, an alkyl group, a halogen atom, an alkoxy group, an acyloxy group, an acyl group, an alkenyl group, an alkynyl group, an aryl group, an alkylthio group, an alkoxycarbonyl group, a carboxy group, an alkylsulfinyl group, an alkylsulfonyl group, an amino group, and an alkylamino group; wherein R_2 and R_3 can be connected in order to form a cycloalkane like cyclopropane, cyclobutane, cyclopentane or cyclohexane;

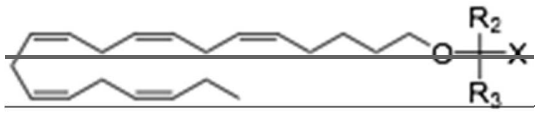
X is a carboxylic acid or a derivative thereof; wherein the derivative is a carboxylate, such as a carboxylic ester; a glyceride; an anhydride; a carboxamide; a phospholipid; or a hydroxymethyl; or a prodrug thereof;

or a pharmaceutically acceptable salt, solvate, or solvate of such a salt thereof,

and at least one additional active agent chosen from a glucagon-like peptide 1 (GLP-1) receptor agonist, an acetyl-CoA carboxylase (ACC) inhibitor, and a farnesoid X receptor (FXR) agonist,

for use in therapeutic and/or prophylactic treatment of fatty liver disease.

92. A combination therapy according to claim 91 for use according to claim 91 wherein the first compound is of Formula (I), and R2, R3, and X are as defined for Formula (II)



(I).

93. A combination therapy according to claim 91 or 92 for use according to claim 91

wherein for the first compound R_2 and R_3 are independently chosen from a hydrogen atom or linear, branched, and/or cyclic C_1-C_6 alkyl groups;

X is a carboxylic acid or a derivative thereof; wherein the derivative is a carboxylate, such as a carboxylic ester; a glyceride; an anhydride; a carboxamide; a phospholipid; or a hydroxymethyl; or a prodrug thereof;

or a pharmaceutically acceptable salt, solvate, or solvate of such salt thereof.

94. The combination therapy according to any one of claims 91 to 93 for use according to claim 91, wherein for the first compound R_2 and R_3 are independently chosen from a hydrogen atom, a methyl group, an ethyl group, a n-propyl group, and an isopropyl group.

95. The combination therapy according to any one of claims 91 to 94 for use according to claim 91, wherein for the first compound R_2 and R_3 are both independently C_1-C_6 alkyl groups.

96. The combination therapy according to any one of claims 91 to 95 for use according to claim 91, wherein for the first compound one of R_2 and R_3 is a hydrogen atom and the other is an ethyl group.

97. The combination therapy according to any one of claims 91 to 96 for use according to claim 91, wherein for the first compound X is a carboxylic acid.

98. The combination therapy according to any one of claims 91 to 96 for use according to claim 91, wherein for the first compound X is a C_1-C_6 alkyl ester.

99. The combination therapy according to claim 98 for use according to claim 91, wherein for the first compound X is chosen from a methyl ester, an ethyl ester, an isopropyl ester, a *n*-butyl ester, and a *tert*-butyl ester.

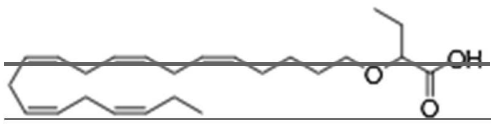
100. The combination therapy according to any one of claims 91, 98 and 99 for use according to claim 91, wherein for the first compound X is selected from the group of a methyl ester and an ethyl ester.

101. The combination therapy according to any one of claims 91 to 96 for use according to claim 91, wherein for the first compound X is a glyceride chosen from a triglyceride, a 1,2-diglyceride, a 1,3-diglyceride, a 1-monoglyceride, and 2-monoglyceride.

102. The combination therapy according to any one of claims 91 to 101 for use according to claim 91, wherein the first compound is present in the form of an enantiomer, diastereomer, or mixture thereof.

103. The combination therapy according to claim 102 for use according to claim 91, wherein the first compound is present in its R form, in its S form or in racemic form.

104. The combination therapy according to claim 91 or 92 for use according to claim 91, wherein the first compound is 2-(((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-yl)oxy)butanoic acid (Compound A), or a pharmaceutically acceptable salt or ester thereof, and the formula is



(Compound A).

105. The combination therapy according to any one of claims 91 to 104 for use according to claim 91, wherein the first compound is administered in a dose of between about 5 mg to about 4 g per dose.

106. The combination therapy according to any one of claims 91 to 105 for use according to claim 91, wherein the first compound is administered once daily.

~~107. The combination therapy according to any one of claims 91 to 106 for use according to claim 91, wherein the additional active agent is chosen from semaglutide, firsocostat, and obeticholic acid (OCA).~~

~~108. The combination therapy according to any one of claims 91 to 106 for use according to claim 91, wherein the additional active agent is semaglutide.~~

~~109. The combination therapy according to any one of claims 91 to 106 for use according to claim 91, wherein the additional active agent is firsocostat.~~

~~110. The combination therapy according to any one of claims 91 to 109 wherein the use treats or reverses fatty liver disease.~~

~~111. The combination therapy according to any one of claims 91 to 110, wherein the use reduces or reverses steatosis.~~

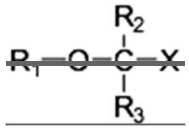
~~112. The combination therapy according to any one of claims 91 to 111, wherein the fatty liver disease is non-alcoholic fatty liver disease (NAFLD).~~

~~113. The combination therapy according to any one of claims 91 to 111, wherein the fatty liver disease is alcoholic fatty liver disease (ALD).~~

~~114. The combination therapy according to any one of claims 91 to 113, wherein the fatty liver disease is not accompanied by an inflammatory response and cellular damage.~~

~~115. The combination therapy according to any one of claims 91 to 114 for use according to claim 91, wherein the compound is 2-(((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-yl)oxy)butanoic acid.~~

~~116. A method of treating fatty liver disease in a subject in need thereof, comprising administering to the subject a pharmaceutically effective amount of a first compound of formula (II):~~



(II)

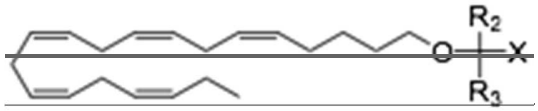
wherein R_1 is selected from a C_{10}-C_{22} alkenyl having 3-6 double bonds;

R_2 and R_3 are the same or different and are selected from the group of a hydrogen atom, a hydroxy group, an alkyl group, a halogen atom, an alkoxy group, an acyloxy group, an acyl group, an alkenyl group, an alkynyl group, an aryl group, an alkylthio group, an alkoxycarbonyl group, a carboxy group, an alkylsulfinyl group, an alkylsulfonyl group, an amino group, and an alkylamino group; wherein R_2 and R_3 can be connected in order to form a cycloalkane like cyclopropane, cyclobutane, cyclopentane or cyclohexane;

X is a carboxylic acid or a derivative thereof; wherein the derivative is a carboxylate, such as a carboxylic ester; a glyceride; an anhydride; a carboxamide; a phospholipid; or a hydroxymethyl; or a prodrug thereof;

or a pharmaceutically acceptable salt, solvate, or solvate of such a salt, thereof; and a pharmaceutically effective amount of at least one additional active agent chosen from a glucagon-like peptide 1 (GLP-1) receptor agonist, an acetyl-CoA carboxylase (ACC) inhibitor, and a farnesoid X receptor (FXR) agonist.

117. The method according to claim 116, wherein the first compound is of Formula (I):



(II).

118. The method according to claim 116 or 117,

wherein for the first compound R_2 and R_3 are independently chosen from a hydrogen atom or linear, branched, and/or cyclic C_1-C_6 alkyl groups; and

X is a carboxylic acid or a derivative thereof; wherein the derivative is a carboxylate, such as a carboxylic ester; a glyceride; an anhydride; a carboxamide; a phospholipid; or a hydroxymethyl; or a prodrug thereof;

or a pharmaceutically acceptable salt, solvate, or solvate of such a salt, thereof.

119. The method according to any one of claims 116 to 118, wherein for the first compound R_2 and R_3 are independently chosen from a hydrogen atom, a methyl group, an ethyl group, an n-propyl group, and an isopropyl group.

120. The method according to any one of claims 116 to 119, wherein for the first compound R_2 and R_3 are both independently C_1-C_6 alkyl groups.

121. The method according to any one of claims 116 to 120, wherein for the first compound one of R_2 and R_3 is a hydrogen atom and the other is an ethyl group.

122. The method according to any one of claims 116 to 121, wherein for the first compound X is a carboxylic acid.

123. The method according to any one of claims 51 to 121, wherein for the first compound X is a C_1-C_6 alkyl ester.

124. The method according to claim 116, wherein for the first compound X is chosen from a methyl ester, an ethyl ester, an isopropyl ester, a *n*-butyl ester, and a *tert*-butyl ester.

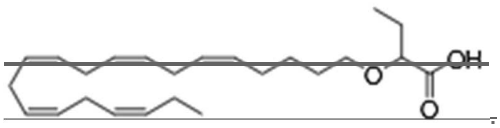
125. The method according to any one of claims 116, 123, or 124 wherein for the first compound X is chosen from a methyl ester and an ethyl ester.

126. The method according to any one of claims 116 to 121, wherein for the first compound X is a glyceride chosen from a triglyceride, a 1,2-diglyceride, a 1,3-diglyceride, a 1-monoglyceride, and 2-monoglyceride.

127. The method according to any one of claims 116 to 61, wherein the first compound is present in the form of an enantiomer, diastereomer, or mixture thereof.

128. The method according to claim 127, wherein the first compound is present in its R form, in its S form, or in racemic form.

129. The method according to claim 116, wherein the first compound is 2-(((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-yl)oxy)butanoic acid (Compound A), or a pharmaceutically acceptable salt or ester thereof, and the formula is



130. The method according to any one of claims 116 to 129, wherein said compound is administered in a dose of between about 5 mg to about 4 g per dose.

131. The method according to any one of claims 116 to 130, wherein the compound is administered once daily.

132. The method according to any one of claims 116 to 131, wherein the additional active agent is chosen from semaglutide, firsocostat, and obeticholic acid (OCA).

133. The method according to any of claims 116 to 132, wherein the additional active agent is semaglutide.

~~134. The method according to any one of claims 116 to 132, wherein the additional active agent is firsocostat.~~

~~135. The method according to any one of claims 116 to 134, wherein the method treats or reverses fatty liver disease.~~

~~136. The method according to any one of claims 116 to 134, wherein the method comprises prophylactically treating fatty liver disease.~~

~~137. The method according to any one of claims 116 to 136, wherein the fatty liver disease is non-alcoholic fatty liver disease (NAFLD).~~

~~138. The method according to any one of claims 116 to 136, wherein the fatty liver disease is alcoholic fatty liver disease (ALD).~~

~~139. The method according to any one of claims 116 to 138, wherein the fatty liver disease is not accompanied by an inflammatory response and cellular damage.~~

~~140. The method according to any one of claims 139, wherein the first compound is 2-(((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-yl)oxy)butanoic acid.~~

~~141. The combination therapies and methods according to any one claims 91 to 140, wherein the first compound is administered at a dosage of about 600 mg daily.~~

~~142. The combination therapies and methods according to any one of claims 91 to 141, wherein the compound is administered at a dosage of about 300 mg daily.~~

~~143. The combination therapies and methods according to any one of claims 91 to 142, wherein hepatic steatosis area is reduced by 70-90%.~~

~~144. The combination therapies and methods according to any one of claims 91 to 143, wherein the percentage of hepatocytes with lipid droplets is reduced by 70-90%.~~

~~145. The combination therapies and methods according to any one of claims 91 to 144, wherein the NAFLD activity (NAS) score is reduced.~~

~~146. The combination therapies and methods according to any one of claims 91 to 145, wherein the steatosis score is reduced.~~