

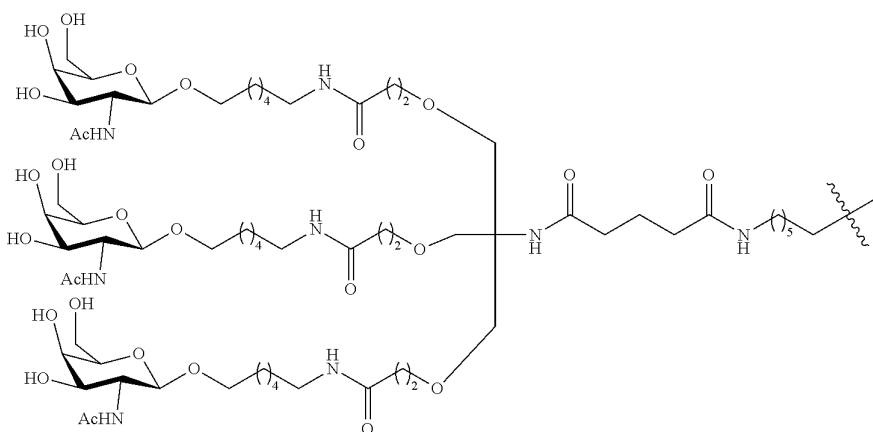
CLAIMS

What is claimed is:

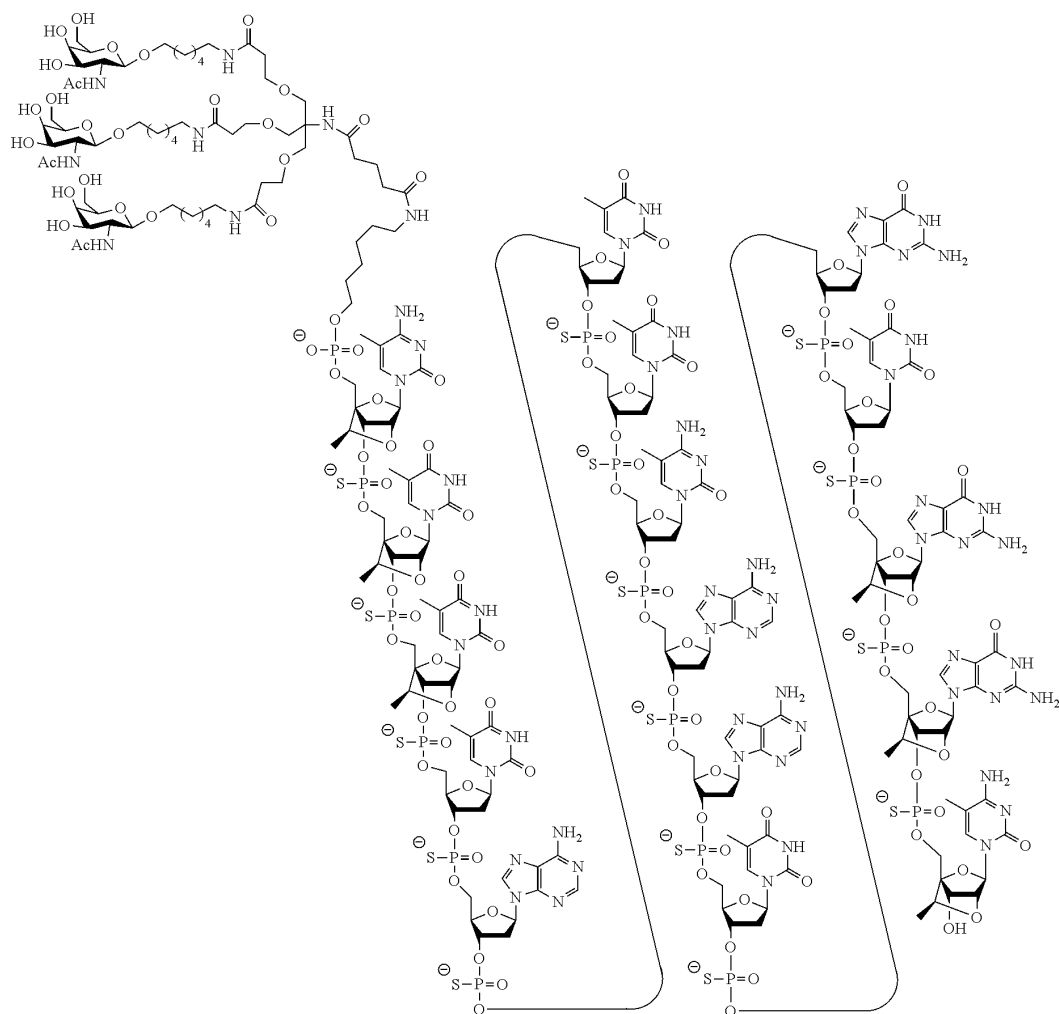
1. Use of an inhibitor of patatin like phospholipase domain containing 3 (PNPLA3) expression in the manufacture of a medicament for treating a liver disease in a subject, wherein the inhibitor of PNPLA3 expression and an agonist of glucagon receptor and/or glucagon-like peptide-1 (GLP-1) receptor are to be administered to the subject, and wherein the inhibitor of PNPLA3 expression is an antisense oligonucleotide that is complementary to a region of a nucleic acid encoding PNPLA3.
2. The use of claim 1, wherein the antisense oligonucleotide is complementary to a site within nucleotides 5567-5731 of the nucleic acid encoding PNPLA3.
3. The use of claim 1, wherein the antisense oligonucleotide is complementary to a site within nucleotides 5644-5731 of the nucleic acid encoding PNPLA3.
4. The use of claim 1, wherein the antisense oligonucleotide is complementary to a site within nucleotides 5567-5642 of the nucleic acid encoding PNPLA3.
5. The use of claim 1, wherein the antisense oligonucleotide is complementary to a site within nucleotides 5567-5620 of the nucleic acid encoding PNPLA3.
6. The use of any of claims 1 to 5, wherein the nucleic acid encoding PNPLA3 is an mRNA.
7. The use of any of claims 1 to 6, wherein the antisense oligonucleotide is from 12 to 30 nucleosides in length.
8. The use of any of claims 1 to 6, wherein the antisense oligonucleotide is from 16 to 30 nucleosides in length.
9. The use of any of claims 1 to 8, wherein the antisense oligonucleotide comprises one or more modified sugar moieties.
10. The use of claim 9, wherein the one or more modified sugar moieties are 2'-deoxy, 2'-O-methyl, 2'-O-methoxymethyl, 2'-O-methoxyethyl, 2'-fluoro, 4'-CH(CH₃)-O-2', 4'-CH₂-O-2', 4'-(CH₂)₂-O-2' or combinations thereof.

11. The use of any of claims 1 to 10, wherein the antisense oligonucleotide comprises one or more modified bases.
12. The use of claim 11, wherein the one or more modified bases are 5-methylcytosine.
13. The use of claim 12, wherein every cytosine in the antisense oligonucleotide is 5-methylcytosine.
14. The use of any of claims 1 to 13, wherein the antisense oligonucleotide comprises one or more non-natural internucleoside linkages.
15. The use of claim 14, wherein the one or more internucleoside linkages are phosphorothioate linkages.
16. The use of claim 15, wherein every internucleoside linkage is a phosphorothioate linkage.
17. The use of any of claims 1 to 16, wherein the antisense oligonucleotide comprises a sequence having at least 8 contiguous bases of any one of SEQ ID NOs: 2, 3, 4, 5, 6, 7, 8, 9 and 10.
18. The use of any of claims 1 to 16, wherein the antisense oligonucleotide comprises one of SEQ ID NOs: 2, 3, 4, 5, 6, 7, 8, 9 and 10.
19. The use of any of claims 1 to 18, wherein the antisense oligonucleotide comprises:
 - a) a gap segment consisting of ten linked deoxynucleosides;
 - b) a 5' wing segment consisting of three linked nucleosides; and
 - c) a 3' wing segment consisting of three linked nucleosides;wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a constrained ethyl sugar, wherein each internucleoside linkage is a phosphorothioate linkage, and wherein each cytosine is a 5-methylcytosine.
20. The use of any of claims 1 to 19, wherein the inhibitor of the PNPLA3 expression further comprises a conjugate group.
21. The use of claim 20, wherein the conjugate group is at the 5' end of the antisense oligonucleotide.

22. The use of claim 20 or 21, wherein the conjugate group is:



23. The use of any of claims 1 to 22, wherein the inhibitor of PNPLA3 expression is a compound of the following formula (SEQ ID NO: 2):



or a pharmaceutically acceptable salt thereof.

24. The use of any of claims 1 to 23, wherein the agonist of glucagon receptor and/or GLP-1 receptor is a peptide.
25. The use of claim 24, wherein the peptide comprises the amino acid sequence:
HX2QGTFTSDX10SX12X13LX15X16X17X18AX20X21FX23X24W LX27X28GX
30 (SEQ ID NO: 25)
wherein,
- (1) X2 is S, X10 is Y, X12 is K, X13 is K, X15 is D, X16 is S, X17 is E, X18 is R, X20 is R, X21 is D, X23 is V, X24 is A, X27 is V, X28 is A, and X30 is G (SEQ ID NO: 14);
 - (2) X2 is S, X10 is K, X12 is E, X13 is Y, X15 is D, X16 is S, X17 is E, X18 is R, X20 is R, X21 is D, X23 is V, X24 is A, X27 is E, X28 is A, and X30 is G (SEQ ID NO: 15);
 - (3) X2 is S, X10 is K, X12 is K, X13 is Y, X15 is E, X16 is G, X17 is Q, X18 is A, X20 is K, X21 is E, X23 is I, X24 is A, X27 is E, X28 is K, and X30 is R (SEQ ID NO: 20);
 - (4) X2 is S, X10 is K, X12 is S, X13 is Y, X15 is D, X16 is S, X17 is R, X18 is S, X20 is R, X21 is D, X23 is V, X24 is A, X27 is E, X28 is A, and X30 is G (SEQ ID NO: 18);
 - (5) X2 is S, X10 is K, X12 is E, X13 is Y, X15 is D, X16 is S, X17 is E, X18 is R, X20 is R, X21 is D, X23 is V, X24 is A, X27 is E, X28 is A, and X30 is G (SEQ ID NO: 33); or
 - (6) X2 is S, X10 is K, X12 is S, X13 is Y, X15 is D, X16 is S, X17 is R, X18 is R, X20 is R, X21 is D, X23 is V, X24 is A, X27 is E, X28 is A, and X30 is G (SEQ ID NO: 19).
26. The use of claim 24, wherein the peptide comprises the amino acid sequence HSQGTFTSDKSEYLDSEARDFVAWLEAGG (SEQ ID NO: 33).
27. The use of any of claims 24 to 26, wherein the peptide further comprises a modification to an amino acid in the amino acid sequence.
28. The use of claim 27, wherein the modification is the addition of an acyl moiety.
29. The use of claim 28, wherein the modification is a palmitoyl moiety on the N(epsilon) group of a lysine residue.

30. The use of claim 29, wherein the palmitoyl group is linked to the lysine via a linker.
31. The use of claim 30, wherein the linker is gamma glutamic acid.
32. The use of any of claims 1 to 31, wherein the inhibitor of PNPLA3 expression and the agonist of glucagon receptor and/or GLP-1 receptor are to be administered concomitantly.
33. The use of any of claims 1 to 31, wherein the inhibitor of PNPLA3 expression and the agonist of glucagon receptor and/or GLP-1 receptor are to be administered within 1 hour of one another.
34. The use of any of claims 1 to 31, wherein the inhibitor of PNPLA3 expression and the agonist of glucagon receptor and/or GLP-1 receptor are to be administered within 24 hours of one another.
35. The use of any of claims 1 to 31, wherein the inhibitor of PNPLA3 expression and the agonist of glucagon receptor and/or GLP-1 receptor are to be administered within 72 hours of one another.
36. The use of any of claims 1 to 31, wherein the inhibitor of PNPLA3 expression and the agonist of glucagon receptor and/or GLP-1 receptor are to be administered within one week of one another.
37. The use of any of claims 1 to 31, wherein the inhibitor of PNPLA3 expression and the agonist of glucagon receptor and/or GLP-1 receptor are to be administered within two weeks of one another.
38. The use of any of claims 1 to 37, wherein the inhibitor of PNPLA3 expression is to be administered parenterally.
39. The use of any of claims 1 to 38, wherein the inhibitor of PNPLA3 expression is to be administered daily, twice daily or three times daily.
40. The use of any of claims 1 to 38, wherein the inhibitor of PNPLA3 expression is to be administered weekly, twice weekly or three times weekly.
41. The use of any of claims 1 to 38, wherein the inhibitor of PNPLA3 expression is to be administered monthly, twice monthly or three times monthly.

42. The use of any of claims 1 to 41, wherein the agonist of glucagon receptor and/or GLP-1 receptor is to be administered parenterally.
43. The use of any of claims 1 to 41, wherein the agonist of glucagon receptor and/or GLP-1 receptor is to be administered daily, twice daily or three times daily.
44. The use of any of claims 1 to 41, wherein the agonist of glucagon receptor and/or GLP-1 receptor is to be administered weekly, twice weekly or three times weekly.
45. The use of any of claims 1 to 41, wherein the agonist of glucagon receptor and/or GLP-1 receptor is to be administered monthly, twice monthly or three times monthly.
46. The use of any of claims 1 to 45, wherein the subject is obese and/or has type 2 diabetes mellitus.
47. The use of any of claims 1 to 46, wherein the liver disease is non-alcoholic fatty liver disease (NAFLD).
48. The use of any of claims 1 to 46, wherein the liver disease is nonalcoholic steatohepatitis.
49. The use of any of claims 1 to 46, wherein the liver disease is liver fibrosis.
50. Use of an inhibitor of patatin like phospholipase domain containing 3 (PNPLA3) expression in the manufacture of a medicament for reducing steatosis in the liver of a subject having a liver disease, wherein the inhibitor of PNPLA3 expression and an agonist of glucagon receptor and/or glucagon-like peptide-1 (GLP-1) receptor are to be administered to the subject, and wherein the inhibitor of PNPLA3 expression is an antisense oligonucleotide that is complementary to a region of a nucleic acid encoding PNPLA3.
51. The use of claim 50, wherein the antisense oligonucleotide is from 12 to 30 nucleosides in length.
52. The use of claim 50, wherein the antisense oligonucleotide is from 16 to 30 nucleosides in length.

53. The use of any of claims 50 to 52, wherein the antisense oligonucleotide comprises a sequence having at least 8 contiguous bases of any one of SEQ ID NOs: 2, 3, 4, 5, 6, 7, 8, 9 and 10.

54. The use of any of claims 50 to 52, wherein the antisense oligonucleotide comprises one of SEQ ID NOs: 2, 3, 4, 5, 6, 7, 8, 9 and 10.

55. The use of any of claims 50 to 54, wherein the antisense oligonucleotide comprises:
a) a gap segment consisting of ten linked deoxynucleosides;
b) a 5' wing segment consisting of three linked nucleosides; and
c) a 3' wing segment consisting of three linked nucleosides;
wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a constrained ethyl sugar; wherein each internucleoside linkage is a phosphorothioate linkage and wherein each cytosine is a 5-methylcytosine.

56. The use of any of claims 50 to 55, wherein the agonist of glucagon receptor and/or GLP-1 receptor is a peptide.

57. The use of claim 56, wherein the peptide comprises the amino acid sequence:
HX2QGTFTSDX10SX12X13LX15X16X17X18AX20X21FX23X24W LX27X28GX
30 (SEQ ID NO:25)

wherein,

- (1) X2 is S, X10 is Y, X12 is K, X13 is K, X15 is D, X16 is S, X17 is E, X18 is R, X20 is R, X21 is D, X23 is V, X24 is A, X27 is V, X28 is A, and X30 is G (SEQ ID NO: 14);
- (2) X2 is S, X10 is K, X12 is E, X13 is Y, X15 is D, X16 is S, X17 is E, X18 is R, X20 is R, X21 is D, X23 is V, X24 is A, X27 is E, X28 is A, and X30 is G (SEQ ID NO: 15);
- (3) X2 is S, X10 is K, X12 is K, X13 is Y, X15 is E, X16 is G, X17 is Q, X18 is A, X20 is K, X21 is E, X23 is I, X24 is A, X27 is E, X28 is K, and X30 is R (SEQ ID NO: 20);
- (4) X2 is S, X10 is K, X12 is S, X13 is Y, X15 is D, X16 is S, X17 is R, X18 is S, X20 is R, X21 is D, X23 is V, X24 is A, X27 is E, X28 is A, and X30 is G (SEQ ID NO: 18);

- (5) X2 is S, X10 is K, X12 is E, X13 is Y, X15 is D, X16 is S, X17 is E, X18 is R, X20 is R, X21 is D, X23 is V, X24 is A, X27 is E, X28 is A, and X30 is G (SEQ ID NO: 33); or
- (6) X2 is S, X10 is K, X12 is S, X13 is Y, X15 is D, X16 is S, X17 is R, X18 is R, X20 is R, X21 is D, X23 is V, X24 is A, X27 is E, X28 is A, and X30 is G (SEQ ID NO: 19).

58. The use of any one of claims 50 to 57, wherein total liver steatosis is reduced in the subject compared to total liver steatosis when the inhibitor of PNPLA3 expression or the agonist of glucagon receptor GLP-1 receptor is to be administered alone.

59. The use of any one of claims 50 to 57, wherein total liver steatosis is reduced in the subject at least 30% compared to total liver steatosis when the inhibitor of PNPLA3 expression or the agonist of glucagon receptor GLP-1 receptor is to be administered alone.

60. The use of any one of claims 50 to 57, wherein total liver steatosis is reduced in the subject at least 30% compared to total liver steatosis when the inhibitor of PNPLA3 expression or the agonist of glucagon receptor GLP-1 receptor is to be administered alone.

61. The use of any of claims 50 to 60, wherein the liver disease is non-alcoholic fatty liver disease (NAFLD).

62. The use of any of claims 50 to 60, wherein the liver disease is nonalcoholic steatohepatitis.

63. The use of any of claims 50 to 60, wherein the liver disease is liver fibrosis.

64. Use of an inhibitor of patatin like phospholipase domain containing 3 (PNPLA3) expression in the manufacture of a medicament for reducing inflammation in the liver of a subject having a nonalcoholic fatty liver disease, wherein the inhibitor of PNPLA3 expression and an agonist of glucagon receptor and/or glucagon-like peptide-1 (GLP-1) receptor are to be administered to the subject, and wherein the inhibitor of PNPLA3 expression is an antisense oligonucleotide that is complementary to a region of a nucleic acid encoding PNPLA3.

65. The use of claim 64, wherein the antisense oligonucleotide is from 12 to 30 nucleosides in length.

66. The use of claim 64, wherein the antisense oligonucleotide is from 16 to 30 nucleosides in length.
67. The use of any of claims 64 to 66, wherein the antisense oligonucleotide comprises a sequence having at least 8 contiguous bases of any one of SEQ ID NOs: 2, 3, 4, 5, 6, 7, 8, 9 and 10.
68. The use of any of claims 64 to 66, wherein the antisense oligonucleotide comprises one of SEQ ID NOs: 2, 3, 4, 5, 6, 7, 8, 9 and 10.
69. The use of any of claims 64 to 68, wherein the antisense oligonucleotide comprises:
- a) a gap segment consisting of ten linked deoxynucleosides;
 - b) a 5' wing segment consisting of three linked nucleosides; and
 - c) a 3' wing segment consisting of three linked nucleosides;
- wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a constrained ethyl sugar; wherein each internucleoside linkage is a phosphorothioate linkage and wherein each cytosine is a 5-methylcytosine.
70. The use of any of claims 64 to 69, wherein the agonist of glucagon receptor and/or GLP-1 receptor is a peptide.
71. The use of claim 70, wherein the peptide comprises the amino acid sequence:
HX2QGTFTSDX10SX12X13LX15X16X17X18AX20X21FX23X24WLX27X28GX
30 (SEQ ID NO:25)
wherein,
- (1) X2 is S, X10 is Y, X12 is K, X13 is K, X15 is D, X16 is S, X17 is E, X18 is R, X20 is R, X21 is D, X23 is V, X24 is A, X27 is V, X28 is A, and X30 is G (SEQ ID NO: 14);
 - (2) X2 is S, X10 is K, X12 is E, X13 is Y, X15 is D, X16 is S, X17 is E, X18 is R, X20 is R, X21 is D, X23 is V, X24 is A, X27 is E, X28 is A, and X30 is G (SEQ ID NO: 15);
 - (3) X2 is S, X10 is K, X12 is K, X13 is Y, X15 is E, X16 is G, X17 is Q, X18 is A, X20 is K, X21 is E, X23 is I, X24 is A, X27 is E, X28 is K, and X30 is R (SEQ ID NO: 20);

- (4) X2 is S, X10 is K, X12 is S, X13 is Y, X15 is D, X16 is S, X17 is R, X18 is S, X20 is R, X21 is D, X23 is V, X24 is A, X27 is E, X28 is A, and X30 is G (SEQ ID NO: 18);
- (5) X2 is S, X10 is K, X12 is E, X13 is Y, X15 is D, X16 is S, X17 is E, X18 is R, X20 is R, X21 is D, X23 is V, X24 is A, X27 is E, X28 is A, and X30 is G (SEQ ID NO: 33); or
- (6) X2 is S, X10 is K, X12 is S, X13 is Y, X15 is D, X16 is S, X17 is R, X18 is R, X20 is R, X21 is D, X23 is V, X24 is A, X27 is E, X28 is A, and X30 is G (SEQ ID NO:19).

72. The use of any one of claims 50 to 56, wherein inflammation in the liver is reduced in the subject at least 50% compared to inflammation in the liver when the inhibitor of PNPLA3 expression or the agonist of glucagon receptor GLP-1 receptor is to be administered alone.

73. Use of an inhibitor of patatin like phospholipase domain containing 3 (PNPLA3) expression in the manufacture of a medicament for reducing liver collagen in a subject having a liver disease, wherein the inhibitor of PNPLA3 expression and an agonist of glucagon receptor and/or glucagon-like peptide-1 (GLP-1) receptor are to be administered to the subject, and
wherein the inhibitor of PNPLA3 expression is an antisense oligonucleotide that is complementary to a region of a nucleic acid encoding PNPLA3.

74. The use of claim 73, wherein the antisense oligonucleotide is from 12 to 30 nucleosides in length.

75. The use of claim 73, wherein the antisense oligonucleotide is from 16 to 30 nucleosides in length.

76. The use of any of claims 73 to 75, wherein the antisense oligonucleotide comprises a sequence having at least 8 contiguous bases of any one of SEQ ID NOs: 2, 3, 4, 5, 6, 7, 8, 9 and 10.

77. The use of any of claims 73 to 75, wherein the antisense oligonucleotide comprises one of SEQ ID NOs: 2, 3, 4, 5, 6, 7, 8, 9 and 10.

78. The use of any of claims 73 to 77, wherein the antisense oligonucleotide comprises:

- a) a gap segment consisting of ten linked deoxynucleosides;
- b) a 5' wing segment consisting of three linked nucleosides; and
- c) a 3' wing segment consisting of three linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a constrained ethyl sugar; wherein each internucleoside linkage is a phosphorothioate linkage and wherein each cytosine is a 5-methylcytosine.

79. The use of any of claims 73 to 78, wherein the agonist of glucagon receptor and/or GLP-1 receptor is a peptide.

80. The use of claim 79, wherein the peptide comprises the amino acid sequence:

HX2QGTFTSDX10SX12X13LX15X16X17X18AX20X21FX23X24W LX27X28GX

30 (SEQ ID NO:25)

wherein,

- (1) X2 is S, X10 is Y, X12 is K, X13 is K, X15 is D, X16 is S, X17 is E, X18 is R, X20 is R, X21 is D, X23 is V, X24 is A, X27 is V, X28 is A, and X30 is G (SEQ ID NO: 14);
- (2) X2 is S, X10 is K, X12 is E, X13 is Y, X15 is D, X16 is S, X17 is E, X18 is R, X20 is R, X21 is D, X23 is V, X24 is A, X27 is E, X28 is A, and X30 is G (SEQ ID NO: 15);
- (3) X2 is S, X10 is K, X12 is K, X13 is Y, X15 is E, X16 is G, X17 is Q, X18 is A, X20 is K, X21 is E, X23 is I, X24 is A, X27 is E, X28 is K, and X30 is R (SEQ ID NO: 20);
- (4) X2 is S, X10 is K, X12 is S, X13 is Y, X15 is D, X16 is S, X17 is R, X18 is S, X20 is R, X21 is D, X23 is V, X24 is A, X27 is E, X28 is A, and X30 is G (SEQ ID NO: 18);
- (5) X2 is S, X10 is K, X12 is E, X13 is Y, X15 is D, X16 is S, X17 is E, X18 is R, X20 is R, X21 is D, X23 is V, X24 is A, X27 is E, X28 is A, and X30 is G (SEQ ID NO: 33); or
- (6) X2 is S, X10 is K, X12 is S, X13 is Y, X15 is D, X16 is S, X17 is R, X18 is R, X20 is R, X21 is D, X23 is V, X24 is A, X27 is E, X28 is A, and X30 is G (SEQ ID NO:19).

81. The use of any one of claims 50 to 80, wherein liver collagen is reduced in the subject at least 25% compared to liver collagen when the inhibitor of PNPLA3 expression or the agonist of glucagon receptor GLP-1 receptor is to be administered alone.
82. The use of any of claims 50 to 81, wherein the subject is obese and/or has type 2 diabetes mellitus.
83. The use of any of claims 50 to 81, wherein the liver disease is nonalcoholic steatohepatitis.
84. The use of any of claims 50 to 81, wherein the liver disease is liver fibrosis.
85. A pharmaceutically acceptable composition comprising:
- i) an inhibitor of patatin like phospholipase domain containing 3 (PNPLA3) expression;
 - ii) an agonist of glucagon receptor and/or glucagon-like peptide-1 (GLP-1) receptor;
 - iii) at least one pharmaceutically acceptable excipient.
86. The composition of claim 85, wherein the inhibitor of PNPLA3 expression is an antisense oligonucleotide that is complementary to a region of a nucleic acid encoding PNPLA3.
87. The composition of claim 86, wherein the antisense oligonucleotide comprises a sequence having at least 8 contiguous bases of any one of SEQ ID NOs: 2, 3, 4, 5, 6, 7, 8, 9 and 10.
88. The composition of claim 86, wherein the antisense oligonucleotide comprises one of SEQ ID NOs: 2, 3, 4, 5, 6, 7, 8, 9 and 10.
89. The composition of any of claims 86 to 88, wherein the antisense oligonucleotide comprises:
- a) a gap segment consisting of ten linked deoxynucleosides;
 - b) a 5' wing segment consisting of three linked nucleosides; and
 - c) a 3' wing segment consisting of three linked nucleosides;
- wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a constrained ethyl sugar;

wherein each internucleoside linkage is a phosphorothioate linkage and wherein each cytosine is a 5-methylcytosine.

90. The composition of any of claims 85 to 89, wherein the agonist of glucagon receptor and/or GLP-1 receptor is a peptide.

91. The composition of claim 90, wherein the peptide comprises the amino acid sequence:
HX2QGTFTSDX10SX12X13LX15X16X17X18AX20X21FX23X24WLX27X28GX
30 (SEQ ID NO:25)

wherein,

- (1) X2 is S, X10 is Y, X12 is K, X13 is K, X15 is D, X16 is S, X17 is E, X18 is R, X20 is R, X21 is D, X23 is V, X24 is A, X27 is V, X28 is A, and X30 is G (SEQ ID NO: 14);
- (2) X2 is S, X10 is K, X12 is E, X13 is Y, X15 is D, X16 is S, X17 is E, X18 is R, X20 is R, X21 is D, X23 is V, X24 is A, X27 is E, X28 is A, and X30 is G (SEQ ID NO: 15);
- (3) X2 is S, X10 is K, X12 is K, X13 is Y, X15 is E, X16 is G, X17 is Q, X18 is A, X20 is K, X21 is E, X23 is I, X24 is A, X27 is E, X28 is K, and X30 is R (SEQ ID NO: 20);
- (4) X2 is S, X10 is K, X12 is S, X13 is Y, X15 is D, X16 is S, X17 is R, X18 is S, X20 is R, X21 is D, X23 is V, X24 is A, X27 is E, X28 is A, and X30 is G (SEQ ID NO: 18);
- (5) X2 is S, X10 is K, X12 is E, X13 is Y, X15 is D, X16 is S, X17 is E, X18 is R, X20 is R, X21 is D, X23 is V, X24 is A, X27 is E, X28 is A, and X30 is G (SEQ ID NO: 33); or
- (6) X2 is S, X10 is K, X12 is S, X13 is Y, X15 is D, X16 is S, X17 is R, X18 is R, X20 is R, X21 is D, X23 is V, X24 is A, X27 is E, X28 is A, and X30 is G (SEQ ID NO:19).

92. The composition of any of claims 85 to 91, wherein the composition is formulated for parenteral administration.

93. A kit comprising:

- i) an inhibitor of patatin like phospholipase domain containing 3 (PNPLA3) expression; and

- ii) an agonist of glucagon receptor and/or glucagon-like peptide-1 (GLP-1) receptor.
94. The kit of claim 93, wherein the inhibitor of PNPLA3 expression is an antisense oligonucleotide that is complementary to a region of a nucleic acid encoding PNPLA3.
95. The kit of claim 94, wherein the antisense oligonucleotide comprises a sequence having at least 8 contiguous bases of any one of SEQ ID NOs: 2, 3, 4, 5, 6, 7, 8, 9 and 10.
96. The kit of claim 94, wherein the antisense oligonucleotide comprises one of SEQ ID NOs: 2, 3, 4, 5, 6, 7, 8, 9 and 10.
97. The kit of any of claims 94 to 96, wherein the antisense oligonucleotide comprises:
- a) a gap segment consisting of ten linked deoxynucleosides;
 - b) a 5' wing segment consisting of three linked nucleosides; and
 - c) a 3' wing segment consisting of three linked nucleosides;
- wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a constrained ethyl sugar; wherein each internucleoside linkage is a phosphorothioate linkage and wherein each cytosine is a 5-methylcytosine.
98. The kit of any of claims 93 to 97, wherein the agonist of glucagon receptor and/or GLP-1 receptor is a peptide.
99. The kit of claim 98, wherein the peptide comprises the amino acid sequence:
HX2QGTFTSDX10SX12X13LX15X16X17X18AX20X21FX23X24WLX27X28GX
30 (SEQ ID NO:25)
wherein,
- (1) X2 is S, X10 is Y, X12 is K, X13 is K, X15 is D, X16 is S, X17 is E, X18 is R, X20 is R, X21 is D, X23 is V, X24 is A, X27 is V, X28 is A, and X30 is G (SEQ ID NO: 14);
 - (2) X2 is S, X10 is K, X12 is E, X13 is Y, X15 is D, X16 is S, X17 is E, X18 is R, X20 is R, X21 is D, X23 is V, X24 is A, X27 is E, X28 is A, and X30 is G (SEQ ID NO: 15);
 - (3) X2 is S, X10 is K, X12 is K, X13 is Y, X15 is E, X16 is G, X17 is Q, X18 is A, X20 is K, X21 is E, X23 is I, X24 is A, X27 is E, X28 is K, and X30 is R (SEQ ID NO: 20);

- (4) X2 is S, X10 is K, X12 is S, X13 is Y, X15 is D, X16 is S, X17 is R, X18 is S, X20 is R, X21 is D, X23 is V, X24 is A, X27 is E, X28 is A, and X30 is G (SEQ ID NO: 18);
- (5) X2 is S, X10 is K, X12 is E, X13 is Y, X15 is D, X16 is S, X17 is E, X18 is R, X20 is R, X21 is D, X23 is V, X24 is A, X27 is E, X28 is A, and X30 is G (SEQ ID NO: 33); or
- (6) X2 is S, X10 is K, X12 is S, X13 is Y, X15 is D, X16 is S, X17 is R, X18 is R, X20 is R, X21 is D, X23 is V, X24 is A, X27 is E, X28 is A, and X30 is G (SEQ ID NO:19).