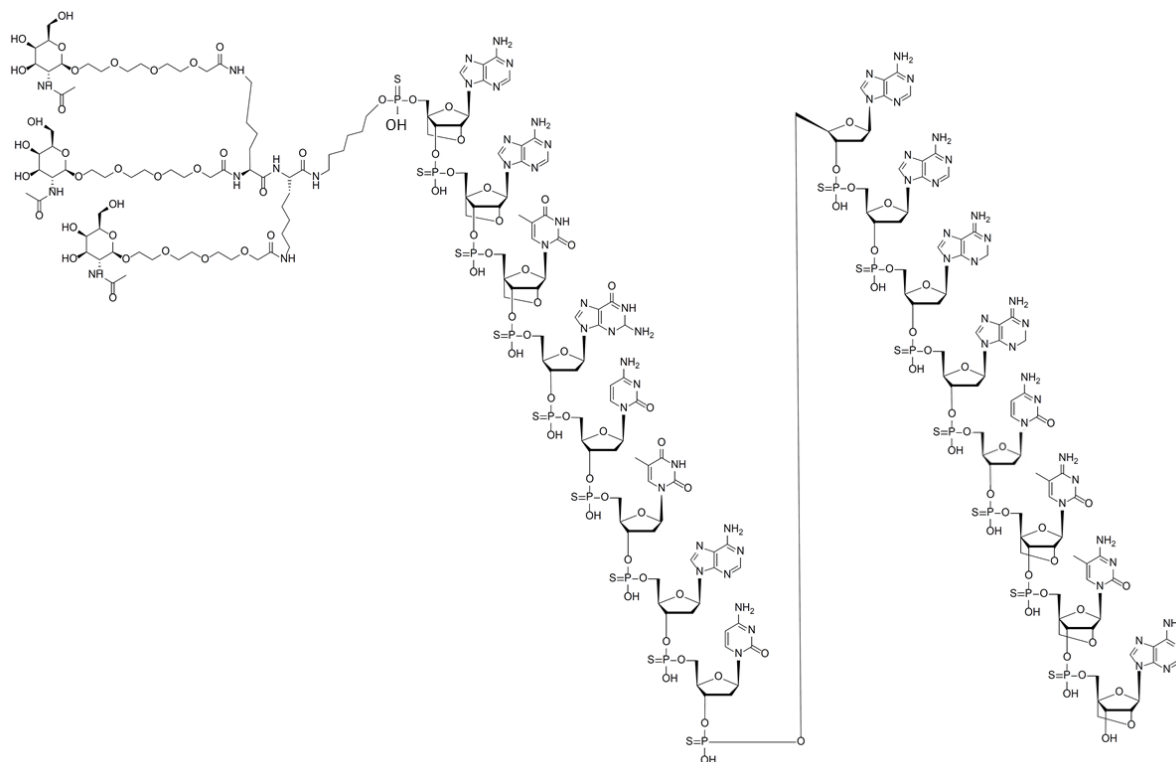


WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising an antisense oligonucleotide of formula I



(Formula I) and N-(5-chlorosalicyloyl)-8-aminocaprylic acid (5-CNAC) or a salt thereof.
~~oligomer and an oral delivery agent, wherein the antisense oligomer is 16 to 22 contiguous nucleotides in length, wherein the sequence of the antisense oligomer comprises a contiguous sequence 16 nucleotides in length which is 100% complementary to a PCSK9 target sequence, wherein the antisense oligomer is a gapmer comprising at least one LNA unit, and wherein the antisense oligomer targets an RNA encoding PCSK9, and wherein the oral delivery agent is covalently or non-covalently attached to the antisense oligomer.~~

- ~~2. The pharmaceutical composition of claim 1, wherein the RNA is a pre-mRNA, splice variant of a pre-mRNA, mature mRNA, or an allelic variant or mutant thereof.~~
- ~~3. The pharmaceutical composition of claim 1, wherein the PCSK9 target sequence is within an exon or an intron.~~

- ~~4. The pharmaceutical composition of claim 1, wherein the PCSK9 target sequence is set forth in SEQ ID NO: 31.~~
- ~~5. The pharmaceutical composition of claim 1, wherein the PCSK9 target sequence comprises a junction between an exon and an intron.~~
- ~~6. The pharmaceutical composition of claim 1, wherein the PCSK9 target sequence is upstream from the 5' end of an open reading frame encoding PCSK9.~~
- ~~7. The pharmaceutical composition of claim 1, wherein the PCSK9 target sequence is downstream from the 3' end of an open reading frame encoding PCSK9.~~
- ~~8. The pharmaceutical composition of claim 1, wherein the LNA is oxy LNA, thio LNA, amino 5 LNA, 5' methyl LNA, ENA, cET, cMOE or a combination thereof.~~
- ~~9. The pharmaceutical composition of claim 1, wherein the LNA is a stereoisomer in the beta-D configuration or the alpha-L configuration.~~
- ~~10. The pharmaceutical composition of claim 1, wherein the antisense oligomer comprises at least one cET unit.~~
- ~~11. The pharmaceutical composition of claim 1, wherein the antisense oligomer comprises 2, 3, 4, 5, 6 or 7 LNA units.~~
- ~~12. The pharmaceutical composition of claim 11, wherein every LNA unit in the antisense oligomer is a stereoisomer in the same configuration.~~
- ~~13. The pharmaceutical composition of claim 11, wherein every LNA unit in the antisense oligomer is a beta-D-oxy LNA unit.~~

- ~~14. The pharmaceutical composition of claim 11, wherein every LNA unit in the antisense oligomer is an alpha-L-oxy-LNA unit.~~
- ~~15. The pharmaceutical composition of claim 1, wherein the sequence of the antisense oligomer comprises at least one phosphorothioate, phosphorodithioate, methylphosphonate, phosphoramidate, or boranophosphate internucleoside linkage.~~
- ~~16. The pharmaceutical composition of claim 15, wherein all the internucleoside linkages are phosphorothioate.~~
- ~~17. The pharmaceutical composition of claim 15, wherein one or more of the internucleoside linkages comprises a chiral center in the R conformation and/or in the S conformation.~~
- ~~18. The pharmaceutical composition of claim 17, wherein all chiral centers are in the R conformation.~~
- ~~19. The pharmaceutical composition of claim 17, wherein all chiral centers are in the S conformation.~~
- ~~20. The pharmaceutical composition of claim 1, wherein the antisense oligomer and an oligomer of SEQ ID NO: 31 can form a duplex with increased thermal stability with respect to a corresponding duplex comprising the corresponding antisense oligomer without LNA.~~
- ~~21. A pharmaceutical composition comprising an antisense oligonucleotide conjugate and an oral delivery agent, wherein the antisense oligonucleotide conjugate comprises:
(i) an antisense oligomer that is 16 to 22 contiguous nucleotides, wherein the sequence of the antisense oligomer comprises a contiguous sequence 16 nucleotides in length which is 100% complementary to a PCSK9 target sequence, and wherein the antisense oligomer is a gapmer comprising at least one LNA unit, and~~

~~(ii) at least one non-nucleotide or non-polynucleotide moiety covalently attached to said antisense oligomer directly or via a linker positioned between the contiguous oligomer sequence and the non-nucleotide or non-polynucleotide moiety,~~

~~wherein the antisense oligonucleotide conjugate targets mRNA encoding PCSK9, and wherein the oral delivery agent is covalently or non-covalently attached to the antisense oligonucleotide conjugate.~~

~~22. The pharmaceutical composition of claim 1, wherein the RNA is a pre-mRNA, splice variant of a pre-mRNA, mature mRNA, or an allelic variant or mutant thereof.~~

~~23. The pharmaceutical composition of claim 1, wherein the PCSK9 target sequence is a sequence within an exon or an intron.~~

~~24. The pharmaceutical composition of claim 1, wherein the PCSK9 target sequence is set forth in SEQ ID NO: 31.~~

~~25. The pharmaceutical composition of claim 1, wherein the PCSK9 target sequence comprises a junction between an exon and an intron.~~

~~26. The pharmaceutical composition of claim 1, wherein the PCSK9 target sequence is upstream from the 5' end of an open reading frame encoding PCSK9.~~

~~27. The pharmaceutical composition of claim 1, wherein the PCSK9 target sequence is downstream from the 3' end of an open reading frame encoding PCSK9.~~

~~28. The pharmaceutical composition of claims 21-27, wherein the non-nucleotide or non-polynucleotide moiety is a liver targeting moiety that is attached to the 5' end or to the 3' end of the antisense oligomer.~~

~~29. The pharmaceutical composition of claims 21-28, wherein the liver targeting moiety is linked to the antisense oligomer via a linker.~~

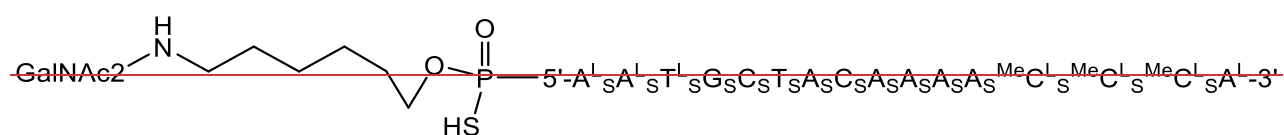
- ~~30. The pharmaceutical composition of claims 21-29, wherein the liver targeting moiety comprises a carbohydrate conjugate moiety comprising a carbohydrate selected from the group consisting of galactose, lactose, N-acetylgalactosamine (GalNAc), mannose, mannose-6-phosphate, and combinations thereof.~~
- ~~31. The pharmaceutical composition of claim 30, wherein the carbohydrate conjugate moiety is not a linear carbohydrate polymer.~~
- ~~32. The pharmaceutical composition of claim 30, wherein the carbohydrate conjugate moiety is a carbohydrate group comprising 1, 2, 3, or 4 carbohydrate moieties.~~
- ~~33. The pharmaceutical composition of claim 32, wherein all the carbohydrate moieties are identical.~~
- ~~34. The pharmaceutical composition of claim 32, wherein at least one carbohydrate moiety is different (non-identical) with respect to the other carbohydrate moieties.~~
- ~~35. The pharmaceutical composition of claim 32, wherein the carbohydrate conjugate moiety comprises at least one asialoglycoprotein receptor targeting conjugate moiety.~~
- ~~36. The pharmaceutical composition of claim 30, wherein the asialoglycoprotein receptor targeting conjugate moiety comprises a monovalent, divalent, trivalent, or tetravalent GalNAc cluster.~~
- ~~37. The pharmaceutical composition of claim 36, wherein each GalNAc in the GalNAc cluster is attached to a branch point group via a spacer.~~
- ~~38. The pharmaceutical composition of claim 37, wherein the branch point group comprises di-lysine.~~
- ~~39. The pharmaceutical composition of claim 37, wherein the spacer comprises a PEG spacer.~~

40. The pharmaceutical composition of claim 30, wherein the linker comprises a C6 to C12 amino-alkyl group or a biocleavable phosphate nucleotide linker comprising between 1 to 6 nucleotides.

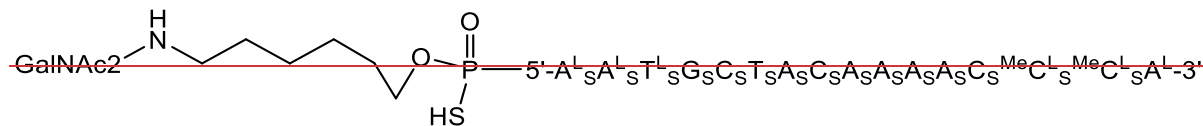
41. The pharmaceutical composition of claim 36, wherein the trivalent GalNAc cluster comprises Conj 1, Conj 2, Conj 1a, or Conj 2a.

42. The pharmaceutical composition of claims 21-41, wherein the non-nucleotide or non-polynucleotide moiety is covalently attached to the antisense oligomer via a covalent bond.

43. A pharmaceutical composition comprising an antisense oligonucleotide conjugate of SEQ ID NO: 18 or SEQ ID NO: 19



SEQ ID 18



SEQ ID 19

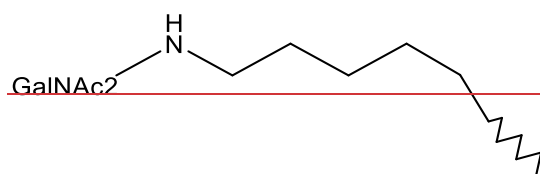
and an oral delivery agent, wherein

a superscript ^L identifies a beta-D-oxy LNA unit,

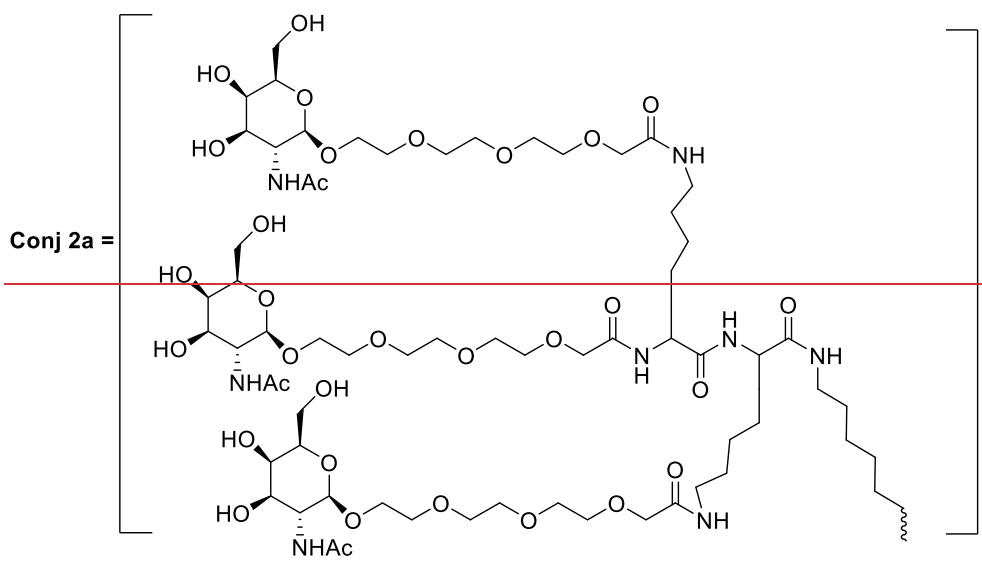
a ^{Me}C identifies a 5-methylcytosine unit,

a subscript s identifies a phosphorothioate internucleoside linkage,

wherein



is a Conj 2a asialoglycoprotein receptor targeting conjugate moiety,



and wherein the antisense oligonucleotide conjugate targets an RNA encoding PCSK9.

44. The pharmaceutical composition of any one of claims 1 to 43, further comprising at least one pharmaceutically acceptable excipient or combination thereof.
45. The pharmaceutical composition of claim 44, wherein the at least one pharmaceutically acceptable excipient or combination thereof is selected from the group consisting of a pH adjuster, a preservative, a flavorant, a taste masking agent, a fragrance, a humectant, a tonicifier, a colorant, a surfactant, a plasticiser, a lubricant, a flow aid, a compression aid, a solubilizer, an excipient, a diluent, a phosphate buffer salt, citric acid, glycol, a dispersing agent, crospovidone, povidone, or any combination thereof.
46. The pharmaceutical composition of any one of claims 1 to 43, further comprising one or more therapeutic agents selected from the group consisting of a statin, ezetimibe, a bile sequestering resin, nicotinic acid, a fibric acid derivative, probucol, neomycin, dextrothyroxine, a plant stanol ester, a cholesterol absorption inhibitor, implitapide, an inhibitor of bile acid transporters, a regulator of hepatic CYP7a, an estrogen replacement therapeutic, and an anti-inflammatory.

- ~~47. The pharmaceutical composition of claim 46, wherein the statin is selected from the group consisting of lovastatin, cerivastatin, pravastatin, atorvastatin, simvastatin, rosuvastatin, and fluvastatin.~~
- ~~48. A method of treating a disease or condition caused by abnormal expression levels and/or activity of PCSK9 in a subject in need thereof comprising administering an effective amount of a pharmaceutical composition of any one of claims 1 to 47 to the subject, wherein the administration of the pharmaceutical composition reduces the level of serum PCSK9 and/or reduces the level of serum LDL cholesterol in the subject.~~
- ~~49. The method of claims 48, wherein PCSK9 is (i) a PCSK9 allelic variant; (ii) a PCSK9 mutant; or, (iii) a PCSK9 splice variant.~~
- ~~50. The method of claim 49, wherein the PCSK9 mutant is a PCSK9 gain of function mutant.~~
- ~~51. The method of claim 48, wherein the disease or condition is selected from the group consisting of atherosclerosis, hypercholesterolemia, HDL/LDL cholesterol imbalance, dyslipidemia, coronary artery disease (CAD), and coronary heart disease (CHD).~~
- ~~52. The method of claim 51, wherein the dyslipidemia is familial hyperlipidemia (FCHL) or acquired hyperlipidemia.~~
- ~~53. The method of claim 51, wherein the hypercholesterolemia is familial hypercholesterolemia or statin resistant hypercholesterolemia.~~
- ~~54. The method of claim 48, further comprising the administration of a therapeutic agent selected from the group consisting of a statin, ezetimibe, a bile sequestering resin, nicotinic acid, a fibric acid derivative, probucol, neomycin, dextrothyroxine, a plant stanol ester, a cholesterol absorption inhibitor, implitapide, an inhibitor of bile acid transporters, a regulator of hepatic CYP7a, an estrogen replacement therapeutic, an anti-inflammatory, or any combination thereof.~~

- ~~55. The method of claim 54, wherein the statin is selected from the group consisting of lovastatin, cerivastatin, pravastatin, atorvastatin, simvastatin, rosuvastatin, and fluvastatin.~~
- ~~56. The method of claim 55, wherein the pharmaceutical composition is administered orally.~~
- ~~57. The method of claim 48, wherein the pharmaceutical composition is administered as a single dose.~~
- ~~58. The method of claim 48, wherein the pharmaceutical composition is administered as multiple doses.~~
- ~~59. A method of treating a disorder selected from the group consisting of atherosclerosis, hyperlipidemia, hypercholesterolemia, HDL/LDL cholesterol imbalance, coronary artery disease (CAD), or coronary heart disease (CHD) in a subject in need thereof, the method comprising administering an effective amount of a pharmaceutical composition of any one of claims 1 to 47 to the subject.~~
- ~~60. An *in vitro* method of reducing expression levels and/or activity of PCSK9 in a cell comprising administering an effective amount of a pharmaceutical composition of any one of claims 1 to 47 to the cell.~~
- ~~61. A method of reducing expression levels and/or activity of PCSK9 in a subject in need thereof comprising administering an effective amount of a pharmaceutical composition of any one of claims 1 to 47 to the subject.~~
- ~~62. A method of reducing cholesterol levels in a subject in need thereof comprising administering to said subject an effective amount of a pharmaceutical composition of any one of claims 1 to claim 47.~~
- ~~63. A method of manufacturing a pharmaceutical composition comprising admixing (i) an antisense oligomer 16 to 22 contiguous nucleotides in length, wherein the sequence of the~~

~~antisense oligomer comprises a contiguous sequence 16 nucleotides in length which is 100% complementary to the sequence of SEQ ID NO: 31, wherein the antisense oligomer is a gapmer comprising at least one LNA unit, and wherein the antisense oligomer targets an RNA encoding PCSK9; and,~~

~~(ii) an oral delivery agent.~~

64. — ~~A method of manufacturing a pharmaceutical composition comprising admixing~~

~~(i) a conjugate comprising (a) an antisense oligomer that is 16 to 22 contiguous nucleotides, wherein the sequence of the antisense oligomer comprises a contiguous sequence 16 nucleotides in length which is 100% complementary to the sequence of SEQ ID NO: 31, and wherein the antisense oligomer is a gapmer comprising at least one LNA unit, and (b) at least one non-nucleotide or non-polynucleotide moiety covalently attached to said antisense oligomer directly or via a linker positioned between the contiguous oligomer sequence and the non-nucleotide or non-polynucleotide moiety, wherein the antisense oligonucleotide conjugate targets an RNA encoding PCSK9; and,~~

~~(ii) an oral delivery agent.~~

65. — ~~The pharmaceutical composition of any one of claims 1 to 47 or the method of any one of claims 48 to 64, wherein the sequence of the antisense oligomer comprises or consists of SEQ ID NO: 26.~~

66. — ~~The pharmaceutical composition of any one of claims 1 to 47 or the method of any one of claims 48 to 64, wherein the sequence of the antisense oligomer comprises or consists of SEQ ID NO: 2 or SEQ ID NO: 3.~~

67. — ~~The pharmaceutical composition of any one of claims 21 to 47 or the method of any one of claims 48 to 64, wherein the sequence of the antisense oligomer conjugate comprises or consists of SEQ ID NO: 18 or SEQ ID NO: 19.~~

68. — ~~The pharmaceutical composition of any one of claims 1 to 47 or 65 to 67, or the method of any one of claims 48 to 67, wherein the oral delivery agent comprises caprylic acid (C8),~~

~~capric acid (C10), a derivative thereof, a pharmaceutically acceptable salt thereof, or any combination thereof.~~

~~69. The pharmaceutical composition of any one of claims 1 to 47 or 65 to 68, or the method of any one of claims 48 to 68, wherein the pharmaceutically acceptable salt is a sodium salt.~~

~~70. The pharmaceutical composition of any one of claims 1 to 47 or 65 to 69, or the method of any one of claims 48 to 69, wherein the pharmaceutical composition is solid.~~

~~71. The pharmaceutical composition of any one of claims 1 to 47 or 65 to 70, or the method of any one of claims 48 to 70, wherein the pharmaceutical composition is in the form of a tablet or a capsule.~~

~~72. The pharmaceutical composition or method of claim 71, wherein the capsule is a liquid capsule.~~

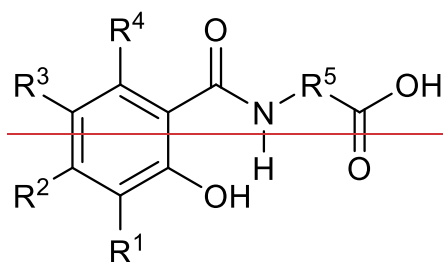
~~73. The pharmaceutical composition of any one of claims 1 to 47 or 65 to 72, or the method of any one of claims 48 to 72, wherein the pharmaceutical composition is enterically coated.~~

~~74. The pharmaceutical composition or method of claim 71, wherein the tablet or capsule is enterically coated.~~

~~75. The pharmaceutical composition or method of claim 71 to 74, wherein the tablet or capsule has a weight between 5 mg and 1000 mg, 10 mg and 500 mg, 10 mg and 250 mg, 100 mg and 200 mg, or 250 mg and 500 mg.~~

~~76. The pharmaceutical composition or method of claim 71 to 75, wherein the amount of antisense oligomer or antisense oligonucleotide conjugate the tablet or capsule is in the range of 1 mg to 100 mg, 5 mg to 100 mg, 10 mg to 100 mg, 20 mg to 100 mg, 20 mg and 50 mg.~~

~~77. The pharmaceutical composition of any one of claims 1 to 47 or 65 to 76, or the method of any one of claims 48 to 76, wherein the oral delivery agent is~~



~~wherein~~

~~R¹, R², R³, and R⁴ are independently hydrogen, —OH, —NR⁶R⁷, halogen, C₁-C₄ alkyl, or C₁-C₄ alkoxy;~~

~~R⁵ is a substituted or unsubstituted C₂-C₁₆ alkylene, substituted or unsubstituted C₂-C₁₆ alkenylene, substituted or unsubstituted C₁-C₁₂ alkyl(arylene), or substituted or unsubstituted aryl(C₁-C₄ alkylene); and~~

~~R⁶ and R⁷ are independently hydrogen, oxygen, or C₁-C₄ alkyl.~~

~~78. The pharmaceutical composition of any one of claims 1 to 47 or 65 to 77, or the method of any one of claims 48 to 77, wherein the delivery agent is selected from the group consisting of N-(8-[2-hydroxybenzoyl]amino)caprylic acid (SNAC), N-(5-chlorosalicyloyl)-8-aminocaprylic acid (5-CNAC), N-(10-[2-hydroxybenzoyl]amino)decanoic acid (SNAD), 4-[(4-chloro-2-hydroxy-benzoyl)amino]butanoic acid (4-CNAB), N-(8-[4-methoxy-chloro-2-hydroxybenzoyl]-amino)-octanoic acid (4-MOAC), 8-(4-hydroxyphenoxy)octanoic acid (4-HPO), 4-m-tolyloxybutyric acid (3-TBA), 4-(3-hydroxyphenylsulfanyl)butyric acid (3-HPSB), 5-phenylpentanoic acid (5-PPA), 8-(2-hydroxyphenoxy)octyldiethanolamine (2-HPOD), (4-isopropylbenzyloxy)acetic acid (4-IBOA), 2-(5-pentanoic acid)-5-(2-hydroxyphenyl)-1,3,4-oxadiazole (2-PHOD), 7-oxo-7-phenylheptanoic acid (7-OPHA), 4-(3-fluorophenylsulfanyl)butyric acid (3-FPSB), or any combination thereof.~~

~~79. The pharmaceutical composition of any one of claims 1 to 47 or 65 to 78, or the method of any one of claims 48 to 78, wherein the oral delivery agent is a salt, hydrate, or solvate of N-(8-(2-hydroxybenzoyl)amino)caprylic acid, or a combination thereof.~~

- ~~80. The pharmaceutical composition or method of claim 79, wherein the salt of N-(8-(2-hydroxybenzoyl)amino)caprylic acid is selected from the group consisting of a sodium salt, a potassium salt, a calcium salt of N-(8-(2-hydroxybenzoyl)amino)caprylic acid, and any combination thereof.~~
- ~~81. The pharmaceutical composition or method of claim 80, wherein the salt of N-(8-(2-hydroxybenzoyl)amino)caprylic acid is sodium salt.~~
- ~~82. The pharmaceutical composition or method of claim 80, wherein the salt of N-(8-(2-hydroxybenzoyl)amino)caprylic acid is a monosodium salt (Salcaprozate sodium 203787-91-1, SNAC, sodium 8-(2-hydroxybenzamido)octanoate).~~
- ~~83. The pharmaceutical composition or method of claim 80, wherein the salt of N-(8-(2-hydroxybenzoyl)amino)caprylic acid is a disodium salt.~~
- ~~84. The pharmaceutical composition of any one of claims 1 to 47 or 65 to 78, or the method of any one of claims 48 to 78, wherein the oral delivery agent is a salt, hydrate, or solvate of N-(5-chlorosalicyloyl)-8-aminocaprylic acid, or a combination thereof.~~
- ~~85. The pharmaceutical composition or method of claim 84, wherein the salt of N-(5-chlorosalicyloyl)-8-aminocaprylic acid is selected from the group consisting of a sodium salt, a potassium salt, a calcium salt of N-(5-chlorosalicyloyl)-8-aminocaprylic acid, and any combination thereof.~~
- ~~86. The pharmaceutical composition or method of claim 85, wherein the salt of N-(5-chlorosalicyloyl)-8-aminocaprylic acid is sodium salt.~~
- 87.2. The pharmaceutical composition ~~or method~~ of claim ~~85~~1, wherein the salt of N-(5-chlorosalicyloyl)-8-aminocaprylic acid is a monosodium salt or a disodium salt.

- ~~88. The pharmaceutical composition or method of claim 85, wherein the salt of N-(5-chlorosalicyloyl)-8-aminocaprylic acid is a disodium salt.~~
- ~~89. The pharmaceutical composition of any one of claims 1 to 47 or 65 to 88, or the method of any one of claims 48 to 88, wherein the oral delivery agent is a salt, hydrate or solvate of capric acid (C10), or a combination.~~
- ~~90. The pharmaceutical composition or method of claim 89, wherein the salt of capric acid (C10) is selected from the group consisting of the sodium salt, potassium salt and calcium salt of capric acid (C10), and any combination thereof.~~
- ~~91. The pharmaceutical composition or method of claim 90, wherein the salt of capric acid (C10) is sodium caprate.~~
- ~~92. The pharmaceutical composition of any one of claims 1 to 47 or 65 to 91, or the method of any one of claims 48 to 91, wherein the pharmaceutical composition is administered from 5 to 60 minutes prior to a meal.~~
- ~~93. The pharmaceutical composition of any one of claims 1 to 47 or 65 to 92, or the method of any one of claims 48 to 91, wherein the pharmaceutical composition is administered from at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55 or 60 minutes prior to a meal.~~
- 94.3. The pharmaceutical composition of ~~any one of claims 1 to 47 or 65 to 93, or the method of any one of claims 48 to 93, wherein the pharmaceutical composition~~ further comprises a pH sensitive coating.
- ~~95. The pharmaceutical composition or method of claim 94, wherein the pH sensitive coating is a pH sensitive polymer.~~
- ~~96. The pharmaceutical composition or method of claim 94, wherein the pH sensitive polymer comprises cellulose, acrylic acid, or a derivative thereof.~~

97.4. The pharmaceutical composition ~~of claim 3 or method of claims 94 to 96~~, wherein the pH sensitive coating comprises a pH-sensitive hydrogel, a pH-activated drug delivery system, a pH-sensitive liposome, micelle or lipid nanoparticle, a pH-sensitive microsphere, a pH-sensitive nanoparticle, or any combination thereof.

5. The pharmaceutical composition of claim 1, further comprising one or more therapeutic agents selected from the group consisting of a statin, ezetimibe, a bile sequestering resin, nicotinic acid, a fibric acid derivative, probucol, neomycin, dextrothyroxine, a plant stanol ester, a cholesterol absorption inhibitor, implitapide, an inhibitor of bile acid transporters, a regulator of hepatic CYP7a, an estrogen replacement therapeutic, and an anti-inflammatory.

6. The pharmaceutical composition of claim 5, wherein the statin is selected from the group consisting of lovastatin, cerivastatin, pravastatin, atorvastatin, simvastatin, rosuvastatin, and fluvastatin.

98.7. A tablet or capsule comprising

(i) (GalNAc)3-amino-hexamethylene- 5' phosphorothioyl)- 2'- O,4'-C-methylene Adenosyl-(3'>5' O,O-phosphorothioyl)- 2'- O,4'-C-methylene Adenosyl -(3'>5' O,O-phosphorothioyl)-2'- O,4'-C-methylene Thymidyl-(3'>5' O,O-phosphorothioyl)- 2'-deoxyGuanosyl-(3'>5' O,O-phosphorothioyl)- 2'-deoxyCytidyl-(3'>5' O,O-phosphorothioyl)-2'-deoxyThymidyl-(3'>5' O,O-phosphorothioyl)- 2'-deoxyAdenosyl-(3'>5' O,O-phosphorothioyl)- 2'-deoxyCytidyl-(3'>5' O,O-phosphorothioyl)- 2'-deoxyAdenosyl-(3'>5' O,O-phosphorothioyl)- 2'-deoxyAdenosyl-(3'>5' O,O-phosphorothioyl)- 2'-deoxyAdenosyl-(3'>5' O,O-phosphorothioyl)- 2'-deoxyAdenosyl-(3'>5' O,O-phosphorothioyl)- 2'-O,4' C-methylene (5-methyl-Cytidyl)-(3'>5' O,O-phosphorothioyl)- 2'-O,4'-C-methylene (5-methyl-Cytidyl)-(3'>5' O,O-phosphorothioyl)- 2' -O,4'-C-methylene Adenosyl hexadeca sodium salt (CIVI 008), and

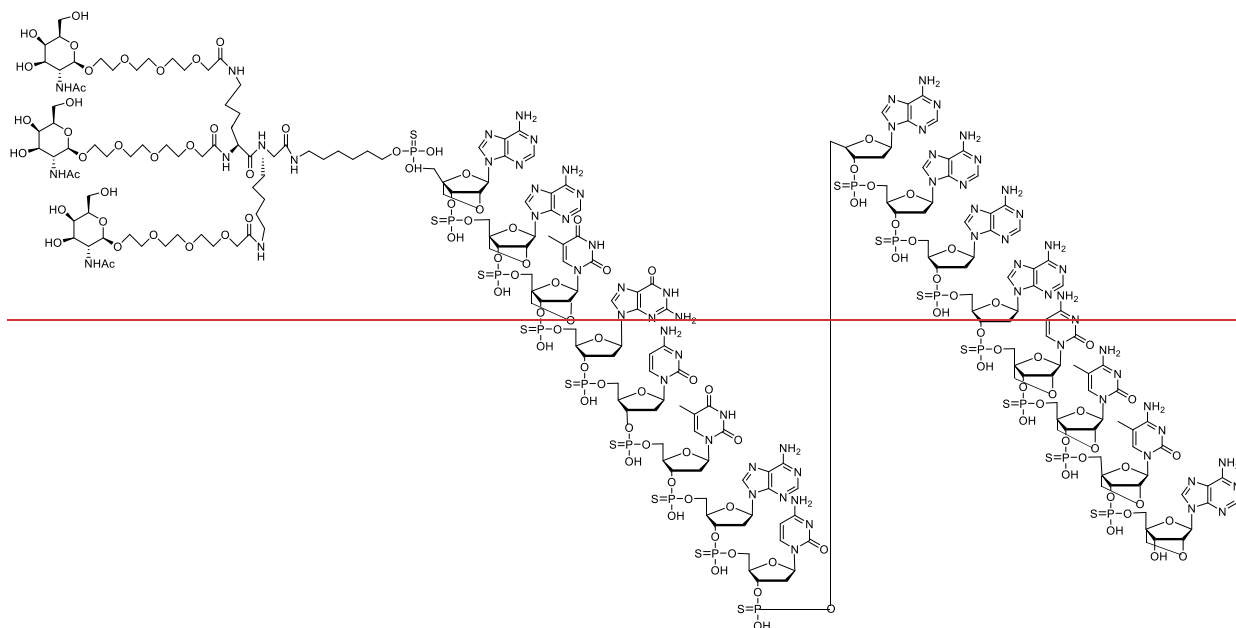
(ii) an 5-CNAC or a salt thereof, wherein the tablet or capsule comprises between 5 and 30 mg of CIVI 008 and between 100 and 200 mg of 5-CNAC,an oral delivery agent

~~selected from the group consisting of SNAC, 5-CNAC, C10, hydrates, solvates, or salts thereof, and combinations thereof; and~~

~~(iii) optionally, a statin.~~

99. — A tablet or capsule comprising

(i) CIVI 008



~~(ii) an oral delivery agent selected from the group consisting of SNAC, 5-CNAC, C10, hydrates, solvates, or salts thereof, and combinations thereof; and~~

~~(iii) optionally, a statin.~~

100. — The tablet or capsule of claim 98 or 99, wherein the oral delivery agent is SNAC.

101. — The tablet or capsule of claim 100, wherein the SNAC is a monosodium salt.

102. — The tablet or capsule of claim 100, wherein the SNAC is a disodium salt.

103. — The tablet or capsule of claim 98 or 99, wherein the oral delivery agent is 5-CNAC.

104.8. The tablet or capsule of claim 1037, wherein 5-CNAC is a monosodium salt, a disodium salt, or a combination thereof.

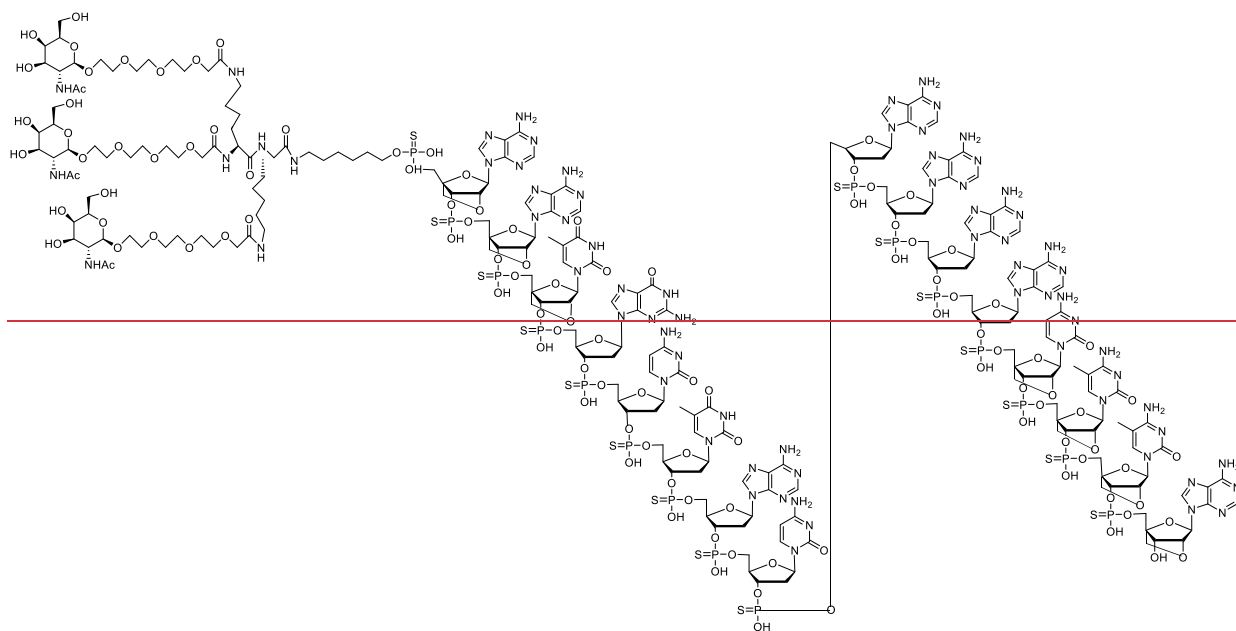
~~105. The tablet or capsule of claim 103, wherein 5-CNAC is a disodium salt.~~

~~106. The tablet or capsule of claim 98 or 99, wherein the oral delivery agent is C10.~~

~~107. The tablet or capsule of claim 98 or 99, wherein the oral delivery agent is C8 or C12.~~

~~108. A capsule comprising~~

~~(i) CIVI 008~~



~~(ii) a 5-CNAC.~~

~~109.9. The tablet or capsule of claim ~~108~~7, where CIVI 008 and 5-CNAC are in a dry blend.~~

~~110.10. The tablet or capsule of claim ~~7~~5 ~~108 or 109~~, wherein the capsule is a gelatin capsule.~~

~~111. The capsule of claim 110, wherein the gel capsule is a hard shell gelatin capsule.~~

~~112.11. The tablet or capsule of ~~any one of claims 108 to 111~~claim 7, wherein the tablet or capsule is enterically coated.~~

~~113. The capsule of any one of claims 108 to 112, wherein the capsule comprises between 5 and 30 mg of CIVI 008 and between 100 and 200 mg of 5-CNAC.~~

~~114.~~12. The tablet or capsule of claim ~~7~~113, wherein the tablet or capsule comprises about 5 mg, about 10 mg, about 20 mg, about 25 mg, or about 30 mg of CIVI 008.

~~115.~~13. The tablet or capsule of ~~any one of claims 108 to 114~~claim 7, wherein the capsule comprises: (i) 10 mg of CIVI 008 and 100 mg of 5-CNAC; (ii) 20 mg of CIVI 008 and 200 mg of 5-CNAC; (iii) 5 mg of CIVI 008 and 200 mg of 5-CNAC; (iv) 10 mg of CIVI 008 and 200 mg of 5-CNAC; (v) 25 mg of CIVI 008 and 200 mg of 5-CNAC; or, (vi) 30 mg of CIVI 008 and 200 mg of 5-CNAC.

- ~~• 10 mg of CIVI 008 and 100 mg of 5-CNAC;~~
- ~~• 20 mg of CIVI 008 and 200 mg of 5-CNAC;~~
- ~~• 5 mg of CIVI 008 and 200 mg of 5-CNAC;~~
- ~~• 10 mg of CIVI 008 and 200 mg of 5-CNAC;~~
- ~~• 25 mg of CIVI 008 and 200 mg of 5-CNAC; or,~~
- ~~• 30 mg of CIVI 008 and 200 mg of 5-CNAC.~~

~~116.~~14. The tablet or capsule of claim 7~~any one of claim 108 to 115~~, further containing a statin.

~~15. The tablet or capsule of claim 7, wherein the tablet or capsule has a weight between 5 mg and 1000 mg, 10 mg and 500 mg, 10 mg and 250 mg, 100 mg and 200 mg, or 250 mg and 500 mg.~~

~~117. A method of treating a disorder selected from the group consisting of atherosclerosis, hyperlipidemia, hypercholesterolemia, HDL/LDL cholesterol imbalance, coronary artery disease (CAD), or coronary heart disease (CHD) in a subject in need thereof, the method comprising administering a capsule of any one of claims 108 to 116 to the subject.~~

~~118. A method of reducing expression levels and/or activity of PCSK9 in a subject in need thereof comprising administering a capsule of any one of claims 108 to 116 to the subject.~~

~~A method of reducing cholesterol levels in a subject in need thereof comprising administering to said subject a capsule of any one of claims 108 to 116.~~

16. The pharmaceutical composition of claim 1 or the tablet or capsule of claim 7 for use in therapy.

~~119.17.~~The pharmaceutical composition of claim 1 or the tablet or capsule of claim 7 ~~A capsule of any one of claims 108 to 116~~ for use in ~~the treatment of~~treating a disorder selected from the group consisting of atherosclerosis, hyperlipidemia, hypercholesterolemia, HDL/LDL cholesterol imbalance, coronary artery disease (CAD), or coronary heart disease (CHD).

~~120.18.~~The pharmaceutical composition of claim 1 or the tablet or capsule of claim 7 ~~A capsule of any one of claims 108 to 116~~ for use as a medicament to reduce expression levels and/or activity of PCSK9 in a subject or to reduce cholesterol levels in a subject.

19. A capsule of any one of claims 108 to 116 for use as a medicament to reduce cholesterol levels in a subject.The tablet or capsule for use according to any one of claims 16 to 18, wherein the tablet or capsule is suitable for administration at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55 or 60 minutes prior to a meal.

~~121.20.~~A method to manufacture a capsule of ~~any one of claims 108 to 116~~claim 7 comprising:
(i) dry blending a first composition comprising CIVI 008 and a second composition comprising 5-CNAC or a salt thereof; and,
(ii) encapsulating the resulting dry blend of step (i) in a capsule.