Claims

1. A pharmaceutical composition comprising a double-stranded ribonucleic acid (dsRNA) molecule ~~at a concentration of about 50 mg/mL to about 200 mg/mL and~~in a phosphate buffered saline (PBS~~)~~),

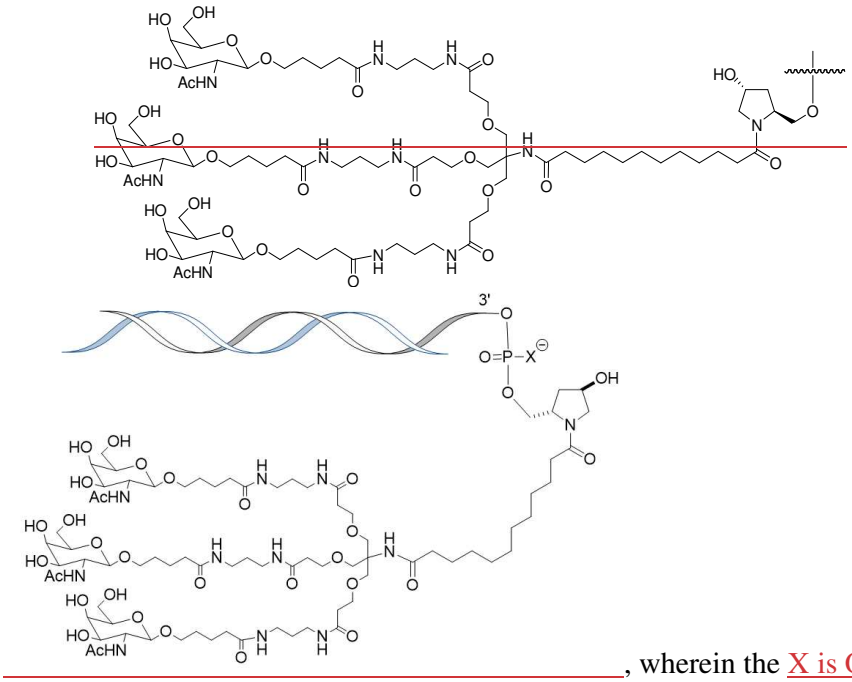
wherein the PBS is at a concentration of ~~about~~ 1 mM to ~~about~~ 10 mM,

wherein the pH and the osmolality of the pharmaceutical composition are suitable for subcutaneous administration to a subject,

wherein the dsRNA molecule ~~comprises~~has a sense strand ~~having~~and an antisense strand, wherein the nucleotide sequence of the sense strand consists of 5'-GfsgsUfuAfaCfaCfCfAfuUfuAfcUfuCfaAf – 3' (SEQ ID NO:~~941~~13) and ~~an antisense strand having~~ the nucleotide sequence of the antisense strand consists of 5'-usUfsgAfaGfuAfaAfuggUfgUfuAfaCfcsasg – 3' (SEQ ID NO:~~960~~14),

wherein a, g, c, and u are 2′-O-methyl (2′-OMe) A, G, C, and U, respectively; Af, Gf, Cf, and Uf are 2′-fluoro A, G, C, and U, respectively; and s is a phosphorothioate linkage, and

wherein a ligand is conjugated to the 3' end of the sense strand ~~via a linker, and wherein the ligand and the linker comprise~~as shown in the following structure:



, wherein the X is O, and wherein the dsRNA molecule is ~~in~~at a free acid form concentration of 50 mg/mL to 200 mg/mL.

2. A pharmaceutical composition comprising a double-stranded ribonucleic acid (dsRNA) molecule ~~at a concentration of about 50 mg/mL to about 200 mg/mL and~~ in a phosphate buffered saline (PBS~~)~~),

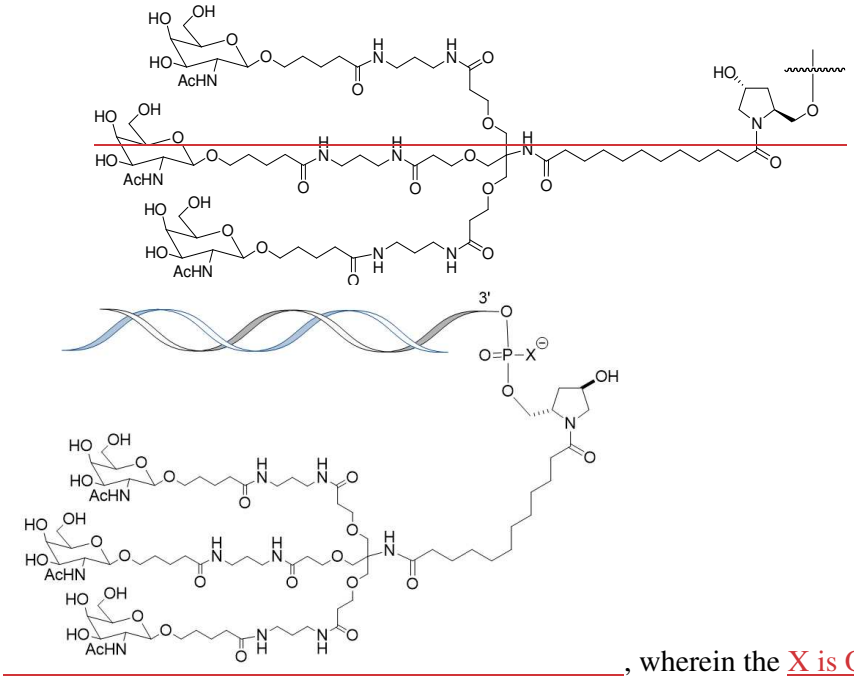
wherein the PBS is at a concentration of ~~about~~ 1 mM to ~~about~~ 10 mM,

wherein the pH and the osmolality of the pharmaceutical composition are suitable for subcutaneous administration to a subject,

wherein the dsRNA molecule ~~comprises~~has a sense strand ~~having~~and an antisense strand, wherein the nucleotide sequence of the sense strand consists of 5'-GfsgsUfuAfaCfaCfCfAfuUfuAfcUfuCfaAf – 3' (ID NO:~~941~~13) and ~~an antisense strand having~~ the nucleotide sequence of the antisense strand consists of 5'-usUfsgAfaGfuAfaAfuggUfgUfuAfaCfcsasg – 3' (SEQ ID NO:~~960~~14),

wherein a, g, c, and u are 2′-O-methyl (2′-OMe) A, G, C, and U, respectively; Af, Gf, Cf, and Uf are 2′-fluoro A, G, C, and U, respectively; and s is a phosphorothioate linkage, ~~and~~

wherein a ligand is conjugated to the 3’ end of the sense strand ~~via a linker, and wherein the ligand and the linker comprise~~ as shown in the following structure:



, wherein the X is O, and wherein the dsRNA molecule is ~~in~~at a salt form concentration of 50 mg/mL to 200 mg/mL.

3. The pharmaceutical composition of claim 2, wherein the salt form is a sodium salt form.

4. The pharmaceutical composition of claim 3, wherein substantially all of the phosphodiester and/or phosphorothiotate groups in the molecule comprise a sodium counterion, optionally wherein all of the phosphodiester and/or phosphorothiotate groups in the molecule comprise a sodium counterion.

5. The pharmaceutical composition of any one of claims 1-4, wherein the concentration of PBS is

(i) between ~~about~~ 2 mM and ~~about~~ 7 mM,

(ii) between ~~about~~ 3 mM and ~~about~~ 6 mM, or

(iii) ~~about~~ 5 mM.

6. The pharmaceutical composition of any one of claims 1-5, wherein the pH of the composition is

(i) between ~~about~~ 5.0 to ~~about~~ 8.0,

(ii) between ~~about~~ 6.0 to ~~about~~ 8.0,

(iii) between ~~about~~ 6.5 to ~~about~~ 7.5, or

(iv) between ~~about~~ 6.8 to ~~about~~ 7.2.

7. The pharmaceutical composition of any one of claims 1-6, wherein the osmolality of the composition is

(i) between ~~about~~ 50 and ~~about~~ 400 mOsm/kg,

(ii) between ~~about~~ 100 and ~~about~~ 400 mOsm/kg,

(iii) between ~~about~~ 240 and ~~about~~ 390 mOsm/kg, or

(iv) between ~~about~~ 290 and ~~about~~ 320 mOsm/kg.

8. The pharmaceutical composition of any one of claims 1-7, wherein the concentration of the dsRNA molecule in the pharmaceutical composition is

(i) between ~~about~~ 50 mg/mL and ~~about~~ 150 mg/mL,

(ii) between ~~about~~ 80 mg/mL and ~~about~~ 110 mg/mL, or

(iii) ~~about~~ 100 mg/mL.

9. A pharmaceutical composition comprising a double-stranded ribonucleic acid (dsRNA) molecule ~~at a concentration of about 100 mg/mL and~~in a phosphate buffered saline (PBS~~) at a concentration of about 5 mM, ~~),

wherein the PBS is at a concentration of 5 mM,

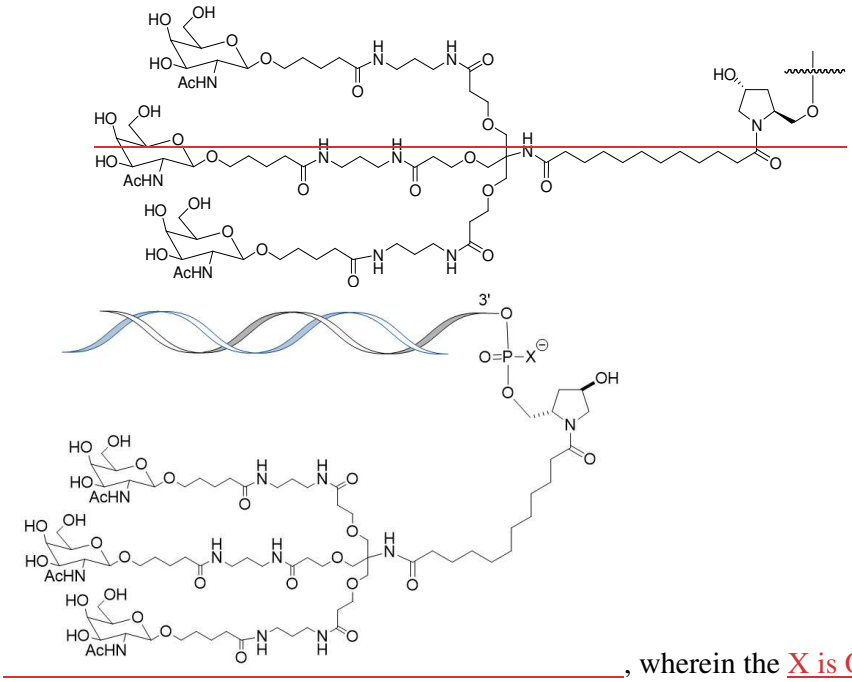
wherein the pH of the pharmaceutical composition is ~~about~~ 6.8 to ~~about~~ 7.2,

wherein the osmolality of the pharmaceutical composition is ~~about~~ 300 mOsm/kg,

wherein the dsRNA molecule ~~comprises~~has a sense strand ~~having~~and an antisense strand, wherein the nucleotide sequence of the sense strand consists of 5'-GfsgsUfuAfaCfaCfCfAfuUfuAfcUfuCfaAf – 3' (SEQ ID NO:~~941~~13) and ~~an antisense strand having~~ the nucleotide sequence of the antisense strand consists of 5'-usUfsgAfaGfuAfaAfuggUfgUfuAfaCfcsasg – 3' (SEQ ID NO:~~960~~14),

wherein a, g, c, and u are 2′-O-methyl (2′-OMe) A, G, C, and U, respectively; Af, Gf, Cf, and Uf are 2′-fluoro A, G, C, and U, respectively; and s is a phosphorothioate linkage, and

wherein a ligand is conjugated to the 3' end of the sense strand ~~via a linker, and wherein the ligand and the linker comprise~~as shown in the following structure:



, wherein the X is O, and wherein the dsRNA molecule is ~~in~~at a free acid form concentration of 100 mg/mL.

10. A pharmaceutical composition comprising a double-stranded ribonucleic acid (dsRNA) molecule ~~at a concentration of about 106 mg/mL and~~ in a phosphate buffered saline (PBS~~)~~),

wherein the PBS is at a concentration of ~~about~~ 5 mM,

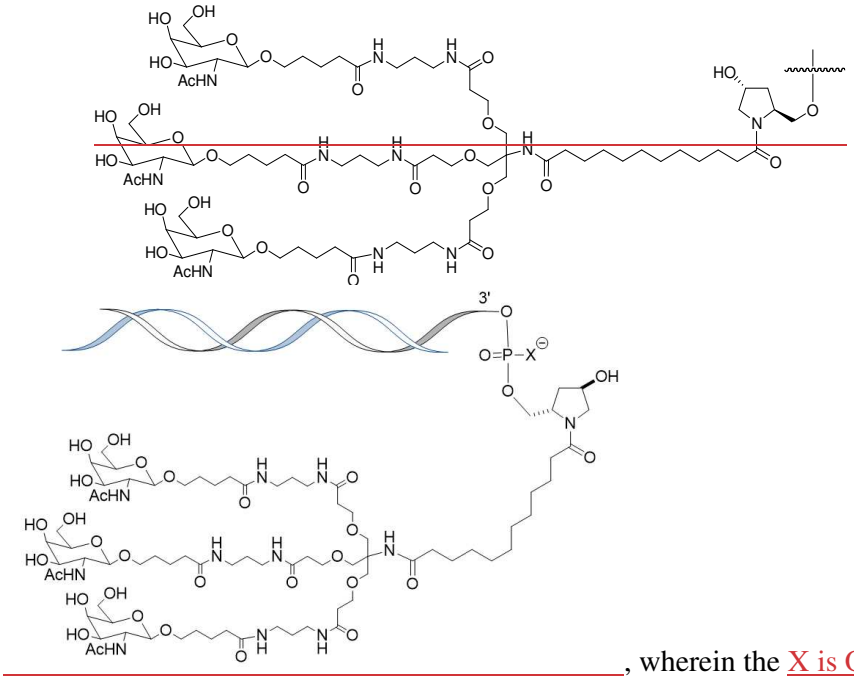
wherein the pH of the pharmaceutical composition is ~~about~~ 6.8 to ~~about~~ 7.2,

wherein the osmolality of the pharmaceutical composition is ~~about~~ 300 mOsm/kg,

wherein the dsRNA molecule ~~comprises~~has a sense strand ~~having~~and an antisense strand, wherein the nucleotide sequence of the sense strand consists of 5'-GfsgsUfuAfaCfaCfCfAfuUfuAfcUfuCfaAf – 3' (SEQ ID NO:~~941~~13) and ~~an antisense strand having~~ the nucleotide sequence of the antisense strand consists of 5'-usUfsgAfaGfuAfaAfuggUfgUfuAfaCfcsasg – 3' (SEQ ID NO:~~960~~14),

wherein a, g, c, and u are 2′-O-methyl (2′-OMe) A, G, C, and U, respectively; Af, Gf, Cf, and Uf are 2′-fluoro A, G, C, and U, respectively; and s is a phosphorothioate linkage, ~~and~~

wherein a ligand is conjugated to the 3’ end of the sense strand ~~via a linker, and wherein the ligand and the linker comprise~~ as shown in the following structure:



, wherein the X is O, and wherein the dsRNA molecule is ~~in~~at a salt form concentration of 106 mg/mL.

11. The pharmaceutical composition of claim 10, wherein the salt form is a sodium salt form.

12. The pharmaceutical composition of claim 11, wherein substantially all of the phosphodiester and/or phosphorothioate groups in the molecule comprise a sodium counterion, optionally wherein all of the phosphodiester and/or phosphorothioate groups in the molecule comprise a sodium counterion.

13. A pharmaceutical composition comprising a double-stranded ribonucleic acid (dsRNA) molecule ~~at a concentration of about 100 mg/mL and~~in a phosphate buffered saline (PBS~~) at a concentration of about 5 mM,~~),

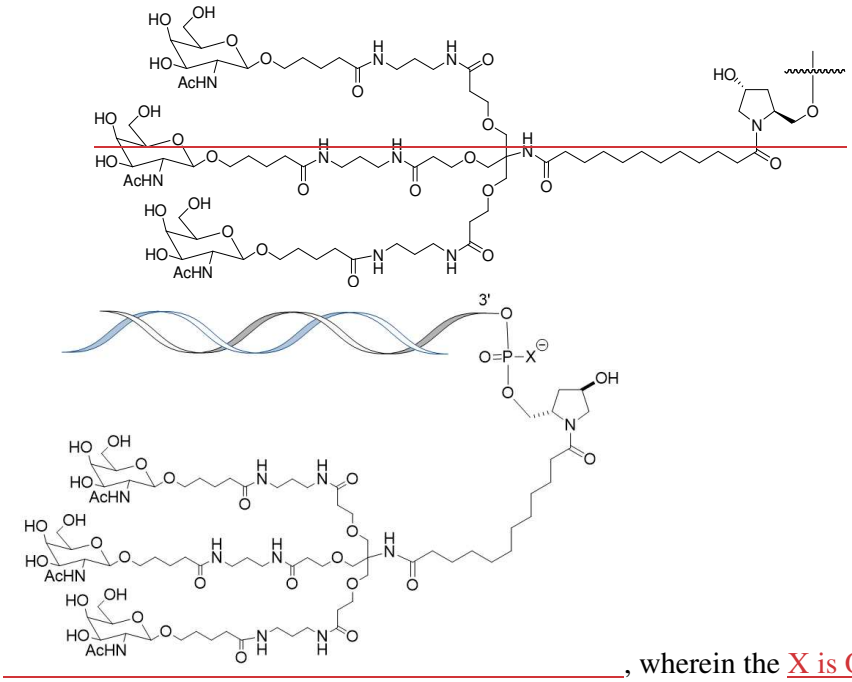
wherein the PBS is at a concentration of 5 mM,

wherein the pH of the pharmaceutical composition is ~~about~~ 6.8 to ~~about~~ 7.2,

wherein the dsRNA molecule ~~comprises~~has a sense strand ~~having~~and an antisense strand, wherein the nucleotide sequence of the sense strand consists of 5'-GfsgsUfuAfaCfaCfCfAfuUfuAfcUfuCfaAf – 3' (SEQ ID NO:~~941~~13) and ~~an antisense strand having~~ the nucleotide sequence of the antisense strand consists of 5'-usUfsgAfaGfuAfaAfuggUfgUfuAfaCfcsasg – 3' (SEQ ID NO:~~960~~14),

wherein a, g, c, and u are 2′-O-methyl (2′-OMe) A, G, C, and U, respectively; Af, Gf, Cf, and Uf are 2′-fluoro A, G, C, and U, respectively; and s is a phosphorothioate linkage, ~~and~~

wherein a ligand is conjugated to the 3' end of the sense strand ~~via a linker, and wherein the ligand and the linker comprise~~ as shown in the following structure:



, wherein the X is O, and wherein the dsRNA molecule is ~~in~~at a free acid form concentration of 100 mg/mL.

14. A pharmaceutical composition comprising a double-stranded ribonucleic acid (dsRNA) molecule ~~at a concentration of about 106 mg/mL and~~ in a phosphate buffered saline (PBS~~)~~),

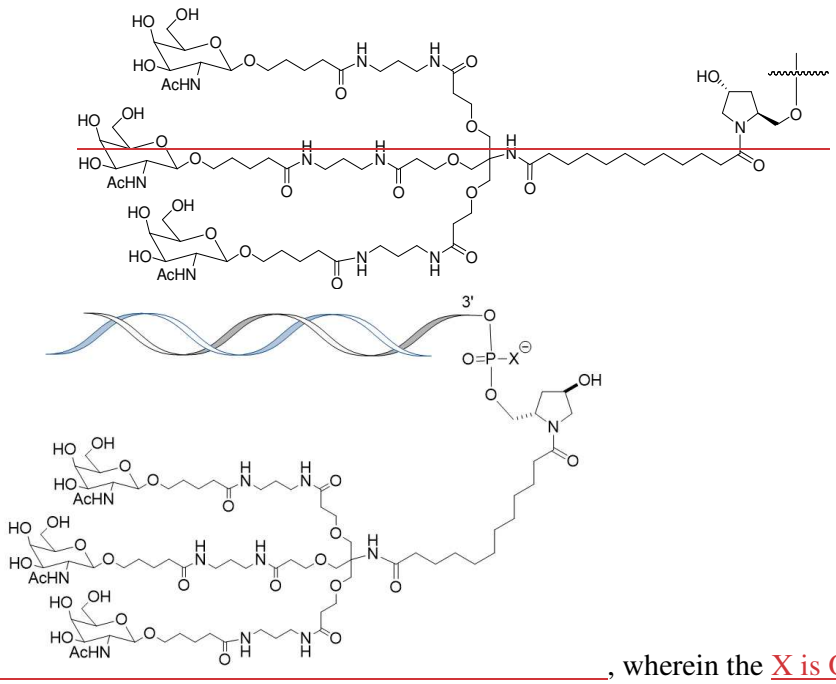
wherein the PBS is at a concentration of ~~about~~ 5 mM,

wherein the pH of the pharmaceutical composition is ~~about~~ 6.8 to ~~about~~ 7.2,

wherein the dsRNA molecule ~~comprises~~has a sense strand ~~having~~and an antisense strand, wherein the nucleotide sequence of the sense strand consists of 5'-GfsgsUfuAfaCfaCfCfAfuUfuAfcUfuCfaAf – 3' (SEQ ID NO:~~941~~13) and ~~an antisense strand having~~ the nucleotide sequence of the antisense strand consists of 5'-usUfsgAfaGfuAfaAfuggUfgUfuAfaCfcsasg – 3' (SEQ ID NO:~~960~~14),

wherein a, g, c, and u are 2′-O-methyl (2′-OMe) A, G, C, and U, respectively; Af, Gf, Cf, and Uf are 2′-fluoro A, G, C, and U, respectively; and s is a phosphorothioate linkage, ~~and~~

wherein a ligand is conjugated to the 3' end of the sense strand ~~via a linker, and wherein the ligand and the linker comprise~~ as shown in the following structure:



, wherein the X is O, and wherein the dsRNA molecule is ~~in~~at a salt form concentration of 106 mg/mL.

15. The pharmaceutical composition of any one of claims 1-14, wherein the composition

(i) is stable for up to ~~about~~ 36 months when stored at ~~about~~ 2°C to ~~about~~ 8°C,

(ii) is stable for up to ~~about~~ 36 months when stored at ~~about~~ 25°C and 60% relative humidity (RH),

(iii) is stable for up to ~~about~~ 6 months when stored at ~~about~~ 40°C and 75% relative humidity (RH),

(iv) comprises not less than (NLT) ~~about~~ 95.0 area % duplex and not more than (NMT) ~~about~~ 5 area% single strands as determined by purity non-denaturing IPRP-HPLC,

(v) comprises not less than (NLT) ~~about~~ 85.0 area % total single strands as determined by purity denaturing AX-HPLC, or

(vi) comprises not less than (NLT) ~~about~~ 80.0 area % total single strands as determined by purity denaturing IPRP-HPLC.

16. A vial comprising the pharmaceutical composition of any one of claims 1-15, optionally wherein

(i) the vial comprises ~~about~~ 0.5 mL to ~~about~~ 2.0 ml of the pharmaceutical composition or

(ii) the vial comprises ~~about~~ 0.8 ml of the pharmaceutical composition.

17. A syringe comprising the pharmaceutical composition of any one of claims 1-15, optionally wherein

(i) the syringe is a 1 ml syringe,

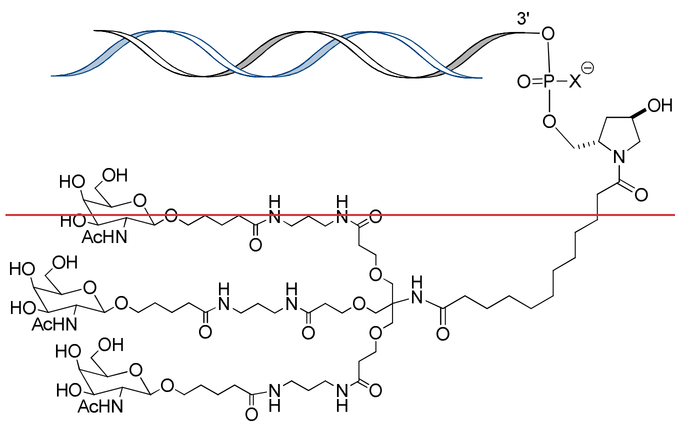
(ii) the syringe is a 3 ml syringe,

(iii) the syringe comprises a 29 G needle,

(iv) the syring comprises a 30 G needle, or

(v) the syringe is a pre-filled syringe.

~~18. The pharmaceutical composition, vial, or syringe of any one of the preceding claims, wherein the ligand is conjugated to the 3' end of the sense strand via the linker as shown in the following structure:~~



~~, wherein the X is O.~~

~~19.~~

18. The pharmaceutical composition, vial, or syringe of any one of claims 1-~~18~~17, wherein the PBS comprises 0.64 mM NaH_2PO_4, ~~about~~ 4.36 mM Na_2HPO_4, and ~~about~~ 84 mM NaCl, optionally pH 7.0.

~~20~~19. The pharmaceutical composition, vial, or syringe of any one of claims 1-~~18~~17, wherein the PBS is obtainable by mixing 0.0885 mg monosodium phosphate monohydrate, 1.169 mg disodium phosphate heptahydrate, and 4.909 mg sodium chloride for every 1 ml of the PBS, optionally pH 7.0.

~~21~~20. The pharmaceutical composition, vial, or syringe of any one of the preceding claims, wherein the pharmaceutical composition is for inhibiting expression of a *SERPINC1* gene.