We Claim:

1. Use of a double stranded ribonucleic acid (RNAi) agent in the manufacture of a medicament for preventing at least one symptom in a human subject having a disorder that would benefit from reduction in Serpinc1 expression, wherein the medicament is to be administered to the subject at a fixed dose of 40 mg to 90 mg of the double stranded ribonucleic acid (RNAi) agent,

wherein the double stranded RNAi agent comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of 5' - UUGAAGUAAAUGGUGUUAACCAG – 3' (SEQ ID NO: 15), wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides, and wherein the sense strand is conjugated to a ligand attached at the 3'-terminus.

2. Use of a double stranded ribonucleic acid (RNAi) agent in the manufacture of a medicament for treating a human subject having a disorder that would benefit from reduction in Serpinc1 expression, wherein the medicament is to be administered to the subject at a fixed dose of 40 mg to 90 mg of the double stranded ribonucleic acid (RNAi) agent,

wherein the double stranded RNAi agent comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of 5' - UUGAAGUAAAUGGUGUUAACCAG – 3' (SEQ ID NO: 15), wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides, and wherein the sense strand is conjugated to a ligand attached at the 3'-terminus.

3. The use of claim 1 or 2, wherein the medicament is to be administered to the subject once a month, once every six weeks, once every 2 months, or quarterly.

4. The use of claim 1 or 2, wherein the medicament is to be administered to the subject as a fixed dose of 50 mg of the double stranded RNAi agent.

5. The use of claim 1 or 2, wherein the medicament is to be administered to the subject as a fixed dose of 80 mg of the double stranded RNAi agent.

6. The use of any one of claims 4-5, wherein the medicament is to be administered subcutaneously.

7. The use of any one of claims 1-6, wherein the use of the medicament lowers Serpinc1 activity in the subject by 70% to 95%.

8. The use of any one of claims 1-7, wherein the use of the medicament increases peak thrombin levels in the subject to within the range of peak thrombin levels in a subject that does not have a disorder that would benefit from reduction in Serpinc1 expression.

9. The use of any one of claims 1-8, wherein the use of the medicament is sufficient to achieve peak thrombin generation levels in the subject to about the same level achieved by administration to the subject of Factor VIII.

10. The use of any one of claims 1-9 wherein the use of the medicament is sufficient to achieve peak thrombin generation levels of greater than about 40% in the subject.

11. The use of any one of claims 1-10, wherein the use of the medicament decreases the annual bleed rate (ABR) of the subject by 80 to about 95% as compared to the median historical on-demand ABR of subjects having a disorder that would benefit from reduction in Serpinc1 expression that are not administered the double stranded RNAi agent.

12. The use of any one of claims 1-11, wherein the disorder is a bleeding disorder.

13. The use of claim 12, wherein the bleeding disorder is an acquired bleeding disorder or an inherited bleeding disorder.

14. The use of claim 12, wherein the bleeding disorder is a hemophilia.

15. The use of claim 14, wherein the hemophilia is hemophilia A, hemophilia B, or hemophilia C; the hemophilia is hemophilia A and the subject is an inhibitor subject; the hemophilia is hemophilia B and the subject is an inhibitor subject; or the hemophilia is hemophilia C and the subject is an inhibitor subject.

16. The use of any one of claims 1-15, wherein the medicament is to be administered subcutaneously.

17. The use of any one of claims 1-16, wherein all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides.

18. The use of any one of claims 1-17, wherein the modified nucleotides are independently selected from the group consisting of a 2'-deoxy-2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, and a non-natural base comprising nucleotide.

19. The use of any one of claims 1-18, wherein the region of complementarity is at least 17 nucleotides in length.

20. The use of any one of claims 1-19, wherein the region of complementarity is between 19 and 21 nucleotides in length.

21. The use of claim 20, wherein the region of complementarity is 19 nucleotides in length.

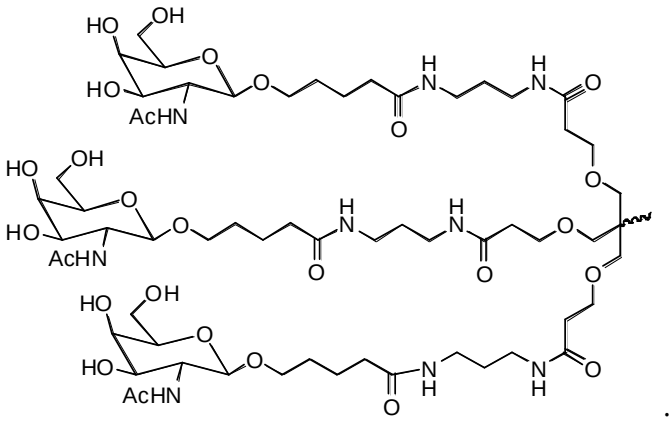
22. The use of any one of claims 1-21, wherein each strand is no more than 30 nucleotides in length.

23. The use of any one of claims 1-22, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide.

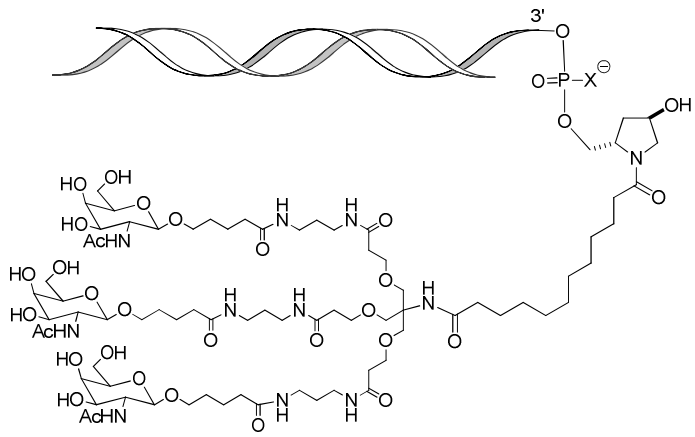
24. The use of any one of claims 1-23, wherein at least one strand comprises a 3' overhang of at least 2 nucleotides.

25. The use of any one of claims 1-24, wherein the ligand is an N-acetylgalactosamine (GalNAc) derivative.

26. The use of any one of claims 1-25, wherein the ligand is



27. The use of claim 26, wherein the double stranded RNAi agent is conjugated to the ligand as shown in the following schematic



and, wherein X is O or S.

28. The use of claim 27, wherein the X is O.

29. The use of any one of claims 1-28, wherein the region of complementarity consists of the nucleotide sequence of 5'-UUGAAGUAAAUGGUGUUAACCAG-3' (SEQ ID NO: 15).

30. The use of any one of claims 1-29, wherein the double stranded RNAi agent comprises a sense strand comprising the nucleotide sequence of 5'- GGUUAACACCAUUUACUUCAA -3' (SEQ ID NO: 16), and an antisense strand comprising the nucleotide sequence of 5'-UUGAAGUAAAUGGUGUUAACCAG-3' (SEQ ID NO: 15).

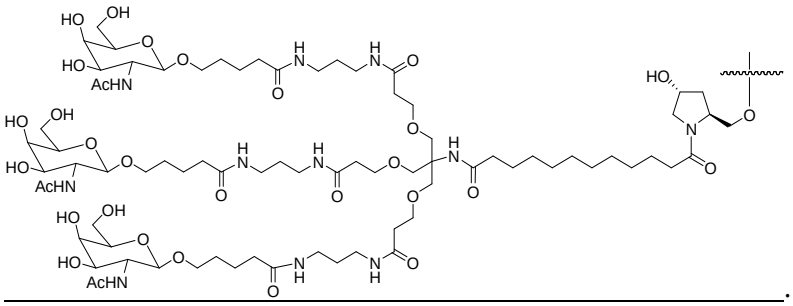
31. The use of claim 30, wherein the sense strand comprises 5’-GfsgsUfuAfaCfaCfCfAfuUfuAfcUfuCfaAf – 3’ (SEQ ID NO:13) and the antisense strand comprises 5’- usUfsgAfaGfuAfaAfuggUfgUfuAfaCfcsasg – 3’ (SEQ ID NO:14),

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

32. The use of any one of claims 1-31,wherein the sense strand comprises 5’-GfsgsUfuAfaCfaCfCfAfuUfuAfcUfuCfaAf – 3’ (SEQ ID NO:13) and the antisense strand comprises 5’- usUfsgAfaGfuAfaAfuggUfgUfuAfaCfcsasg – 3’ (SEQ ID NO:14),

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

wherein the sense strand is conjugated to the ligand as shown in the following schematic



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33. The use of any one of claims 1-32, wherein the medicament is a pharmaceutical composition.

34. The use of claim 33, wherein the pharmaceutical composition comprises an unbuffered solution.

35. The use of claim 34, wherein the unbuffered solution is saline or water.

36. The use of claim 33, wherein the pharmaceutical composition comprises a buffer solution.

37. The use of claim 36, wherein the buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof.

38. The use of claim 37, wherein the buffer solution is phosphate buffered saline (PBS).

39. A kit for use in preventing at least one symptom in a human subject having a disorder that would benefit from reduction in Serpinc1 expression, comprising

a) a medicament comprising a double stranded RNAi agent, wherein the RNAi agent is to be administered to the subject as a fixed dose of 40 mg to 90 mg,

wherein the double stranded RNAi agent comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of 5' - UUGAAGUAAAUGGUGUUAACCAG – 3' (SEQ ID NO: 15), wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides, and wherein the sense strand is conjugated to a ligand attached at the 3'-terminus, and

b) instructions for use, and

c) optionally, means for administering the medicament to the subject.

40. A kit for use in treating a human subject having a disorder that would benefit from reduction in Serpinc1 expression, comprising

a) a medicament comprising a double stranded RNAi agent, wherein the RNAi agent is to be administered to the subject as a fixed dose of 40 mg to 90 mg,

wherein the double stranded RNAi agent comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of 5' - UUGAAGUAAAUGGUGUUAACCAG – 3' (SEQ ID NO: 15), wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides, and wherein the sense strand is conjugated to a ligand attached at the 3'-terminus, and

b) instructions for use, and

c) optionally, means for administering the medicament to the subject.

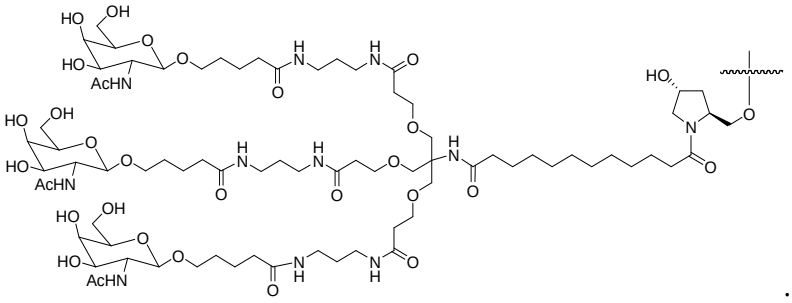
41. Use of a double stranded ribonucleic acid (RNAi) agent in the manufacture of a medicament for preventing at least one symptom in a human subject having a hemophilia, wherein the medicament is to be subcutaneously administered to the subject once every month at a fixed dose of 80 mg of the double stranded ribonucleic acid (RNAi) agent,

wherein the double stranded RNAi agent comprises a sense strand and an antisense strand forming a double stranded region, and

wherein the sense strand consists of 5’-GfsgsUfuAfaCfaCfCfAfuUfuAfcUfuCfaAf – 3’ (SEQ ID NO:13) and the antisense strand consists of 5’- usUfsgAfaGfuAfaAfuggUfgUfuAfaCfcsasg – 3’ (SEQ ID NO:14),

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

wherein a ligand is conjugated to the 3’ end of the sense strand, and wherein the ligand has the following structure:



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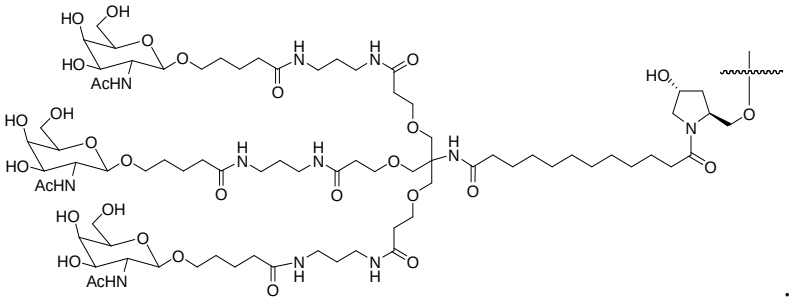
42. Use of a double stranded ribonucleic acid (RNAi) agent in the manufacture of a medicament for treating a human subject having a hemophilia, wherein the medicament is to be subcutaneously administered to the subject once every month at a fixed dose of 80 mg of the double stranded ribonucleic acid (RNAi) agent,

wherein the double stranded RNAi agent comprises a sense strand and an amtisense strand forming a double stranded region, and

wherein the sense strand consists of 5’-GfsgsUfuAfaCfaCfCfAfuUfuAfcUfuCfaAf – 3’ (SEQ ID NO:13) and the antisense strand consists of 5’- usUfsgAfaGfuAfaAfuggUfgUfuAfaCfcsasg – 3’ (SEQ ID NO:14),

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

wherein a ligand is conjugated to the 3’ end of the sense strand, and wherein the ligand has the following structure:



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43. A kit for use in preventing at least one symptom in a human subject having a hemophilia, comprising

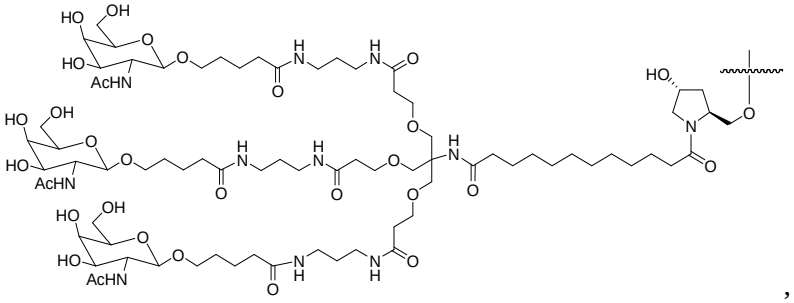
a) a medicament comprising a double stranded RNAi agent, wherein the RNAi agent is to be subcutaneously administered to the subject as a fixed dose of 80 mg,

wherein the double stranded RNAi agent comprises a sense strand and an antisense strand forming a double stranded region, and

wherein the sense strand consists of 5'- GfsgsUfuAfaCfaCfCfAfuUfuAfcUfuCfaAf – 3' (SEQ ID NO:13) and the antisense strand consists of 5'- usUfsgAfaGfuAfaAfuggUfgUfuAfaCfcsasg – 3' (SEQ ID NO:14),

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

wherein a ligand is conjugated to the 3' end of the sense strand, and wherein the ligand has the following structure:



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b) instructions for use, and

c) optionally, means for administering the medicament to the subject.

44. A kit for use in treating a human subject having a hemophilia, comprising

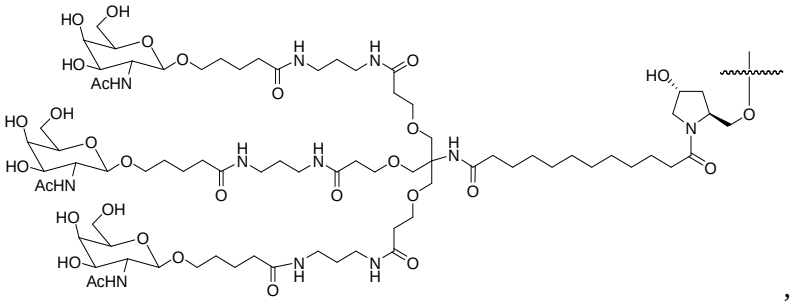
a) a medicament comprising a double stranded RNAi agent, wherein the RNAi agent is to be subcutaneously administered to the subject as a fixed dose of 80 mg,

wherein the double stranded RNAi agent comprises a sense strand and an amtisense strand forming a double stranded region, and

wherein the sense strand consists of 5'- GfsgsUfuAfaCfaCfCfAfuUfuAfcUfuCfaAf – 3' (SEQ ID NO:13) and the antisense strand consists of 5'- usUfsgAfaGfuAfaAfuggUfgUfuAfaCfcsasg – 3' (SEQ ID NO:14),

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

wherein a ligand is conjugated to the 3’ end of the sense strand, and wherein the ligand has the following structure:



, and

b) instructions for use, and

c) optionally, means for administering the medicament to the subject.