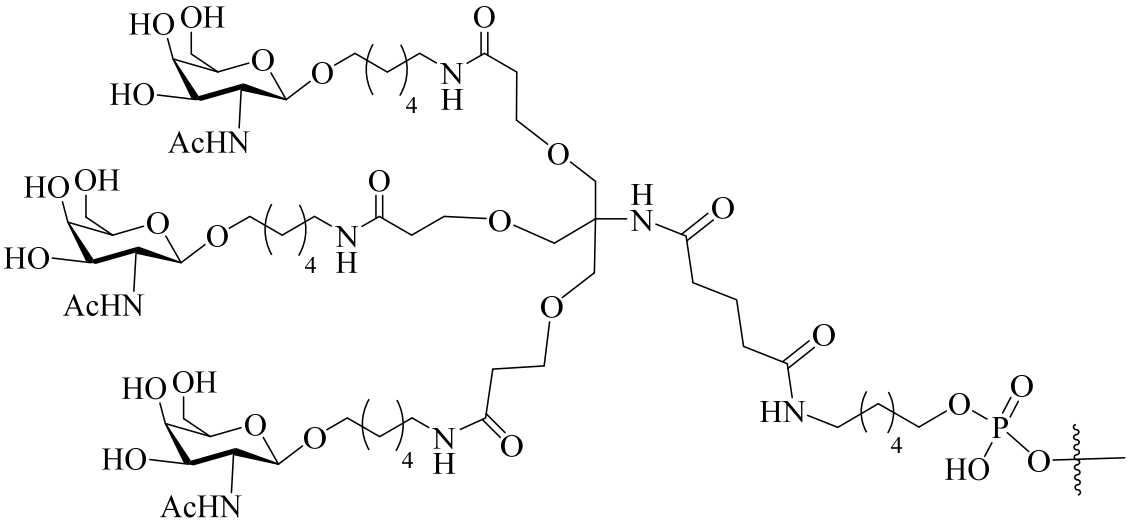
Embodiment 4. An oligomeric compound comprising a modified oligonucleotide according to the following formula:

(THA-GalNAc$_3$)o Aes mCeo Geo Geo mCeo Ads Tds Tds Gds Gds Tds Gds mCds Ads mCds Aeo Geo Tes Tes Te (SEQ ID NO: 3); wherein, (THA-GalNAc3)o is represented by the following structure:



and wherein,

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'- $OCH_2CH_2OCH_3$ ribosyl sugar moiety,

d = a 2'-deoxyribosyl sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage;

or a salt thereof.

Embodiment 5. The oligomeric compound of any one of embodiments 1, 3 or 5, which is a sodium salt.

Embodiment 6. A chirally enriched population of the oligomeric compound of any of embodiments 1-5 wherein the population is enriched for oligomeric compounds having a modified oligonucleotide comprising at least one particular phosphorothioate internucleoside linkage having a particular stereochemical configuration.

Embodiment 7. The chirally enriched population of embodiment 6, wherein the population is enriched for oligomeric compounds having a modified oligonucleotide comprising at least one particular phosphorothioate internucleoside linkage having the (Sp) configuration.

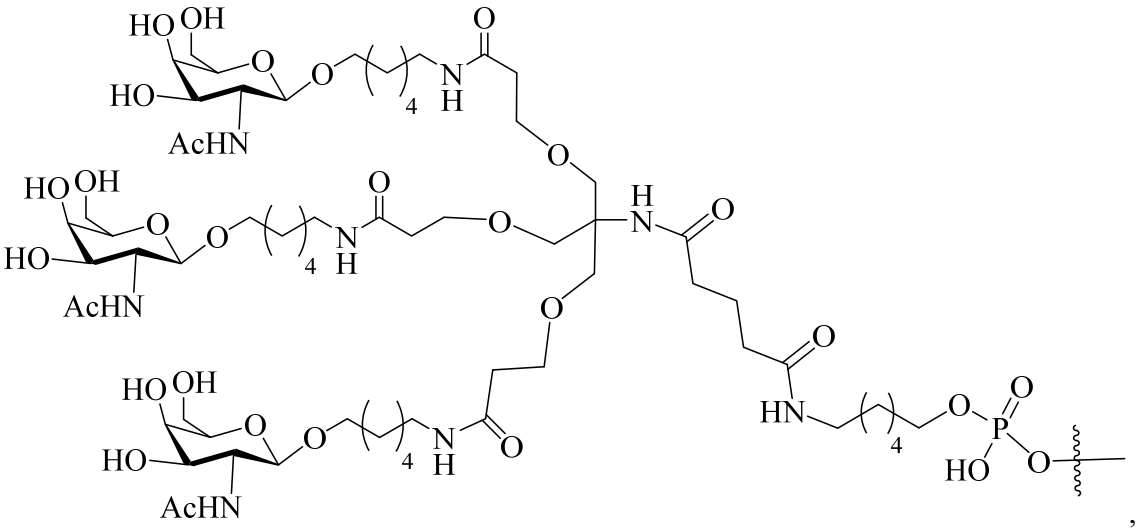
53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%.

In certain embodiments, pharmaceutical compositions and methods described herein are efficacious because they improve a cardiovascular outcome in an animal. In certain embodiments, pharmaceutical compositions and methods improve a cardiovascular outcome in a population treated with a pharmaceutical composition disclosed herein and/or according to a method disclosed herein relative to a population that is not treated with the pharmaceutical composition and/or according to the method. In certain embodiments, the improved cardiovascular outcome is a reduction of the risk of developing a thromboembolic condition. In certain embodiments, the improved cardiovascular outcome is a reduction in the occurrence of one or more major cardiovascular events. Cardiovascular events include, but are not limited to, death, myocardial infarction, reinfarction, stroke, cardiogenic shock, pulmonary edema, cardiac arrest, and atrial dysrhythmia. In certain embodiments, the cardiovascular event is an ischemic stroke. In certain embodiments, the cardiovascular event is a peripheral arterial ischemic event, *e.g.*, amputation ischemia or limb ischemia. In certain embodiments, the improved cardiovascular outcome is evidenced by improved carotid intimal media thickness. In certain embodiments, improved carotid intimal media thickness is a decrease in thickness. In certain such embodiments, improved carotid intimal media thickness is a prevention an increase of intimal media thickness.

XII. Certain Comparator Compositions

In certain embodiments, Compound No: 416858, a 5-10-5 MOE gapmer, having a sequence of (from 5' to 3') ACGGCATTGGTGCACAGTTT (incorporated herein as SEQ ID NO: 3), wherein each internucleoside linkage is a phosphorothioate internucleoside linkage, each cytosine is a 5-methyl cytosine, and each of nucleosides 1-5 and 16-20 (from 5' to 3') comprise a 2'-MOE modified sugar, which was previously described in WO 2010/045509, incorporated herein by reference, is a comparator compound. Compound No. 416858 was selected as a comparator compound because it was selected for clinical development and was confirmed to be tolerable in phase 1 clinical trials, and is currently in phase 2 clinicals. See, e.g., BETHUNE, et al, "Pharmacokinetics and Pharmacodynamics of Ionis-FXI_{Rx}, an Antisense Inhibitor of Factor XI, in Patients with End-Stage Renal Disease on Hemodialysis," *Blood* (2017)130:1116; BÜLLER, et al, "Factor XI antisense oligonucleotide for prevention of venous thrombosis." *N Engl J Med* (2015) 372(3): 232-240 and LIU, et al, "ISIS-FXI_{Rx}, A Novel and Specific Antisense Inhibitor of Factor XI, Caused Significant Reduction in FXI Antigen and Activity and Increased aPTT without Causing Bleeding in Healthy Volunteers" *Blood* (2011)118:209.

In certain embodiments, Compound No. 957943 described herein, is superior relative to Compound No. 416858 because it demonstrates one or more improved properties, such as, potency and tolerability. Compound No. 957943 may be dosed at lower amounts than Compound No. 416858. Compound No.

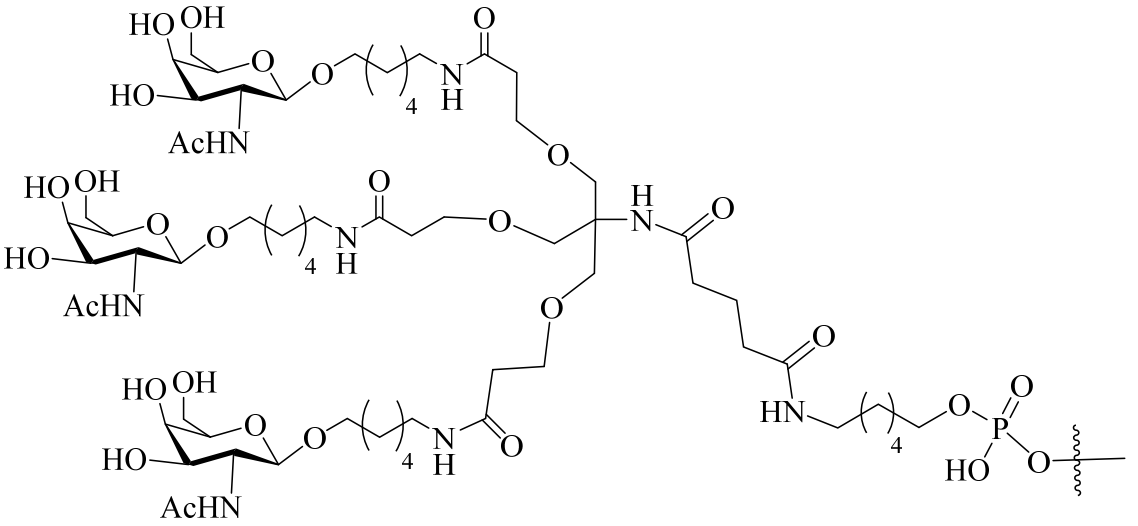


,

and wherein the modified oligonucleotide is a 5-10-5 MOE gapmer, having a sequence of (from 5' to 3') ACGGCATTGGTGCACAGTTT (incorporated herein as SEQ ID NO: 3), wherein each of nucleosides 1-5 and 16-20 (from 5' to 3') comprise a 2'-MOE modification and each of nucleosides 6-15 are 2'-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 5 to 6, 16 to 17, and 17 to 18 are phosphodiester internucleoside linkages and the internucleoside linkages between nucleosides 1 to 2, 6 to 7, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 957943 is characterized by the following chemical notation: (THA-GalNAc$_3$)o Aes mCeo Geo Geo mCeo Ads Tds Tds Gds Gds Tds Gds mCds Ads mCds Aeo Geo Tes Tes Te; wherein,

(THA-GalNAc3)o is represented by the following structure:



and wherein,

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

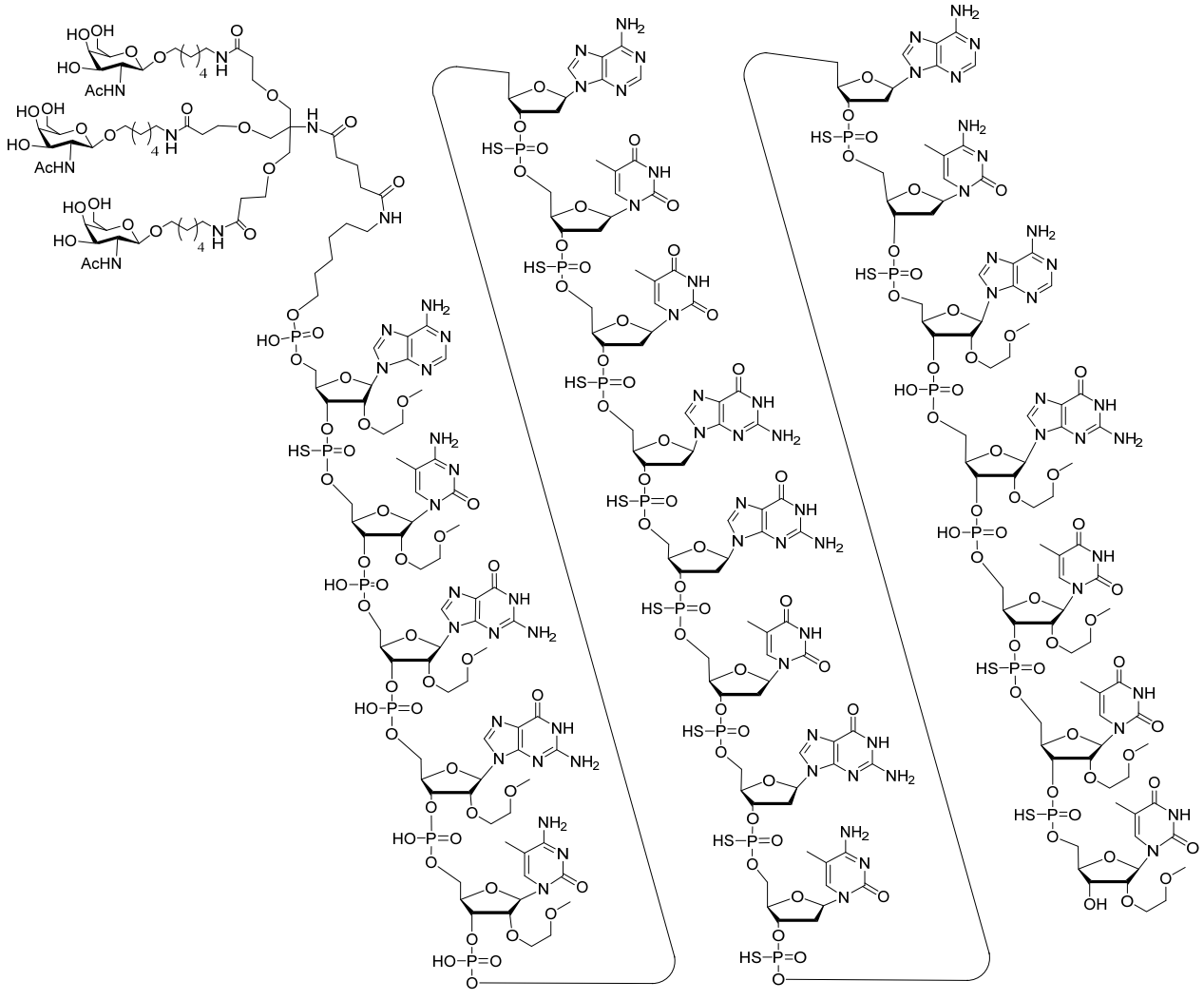
e = a 2'- $OCH_2CH_2OCH_3$ ribosyl sugar moiety,

d = a 2'-deoxyribosyl sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

In certain embodiments, Compound No. 957943 is represented by the following chemical structure:



Structure 1. Compound No. 957943 (SEQ ID NO: 3)

Oligomeric compounds No. 416858 and 957943 were tested in a Factor XI PAC transgenic mouse model which uses bacterial P1 artificial chromosome (PAC) containing the entire WT human Factor XI gene. The mouse model was generated from a human FXI gene fragment containing the entire ~24 Kb human FXI transgene as well as 9Kb upstream and 6Kb downstream. The gene fragment was microinjected into the pronucleus of fertilized mouse eggs, and the complete BAC integration of the transgene was confirmed by PCR using human specific primer probe sets. The established founder has predominate liver expression of human FXI RNA and circulating human FXI in plasma.

Table 1. Oligomeric compounds complementary to human FXI

Compound Number	5' modification	Chemistry notation (5' to 3')	SEQ ID NO:
416858	none	$A_{es}{}^{m}C_{es}G_{es}G_{es}{}^{m}C_{es}A_{ds}T_{ds}T_{ds}G_{ds}G_{ds}T_{ds}G_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}A_{es}G_{es}T_{es}T_{es}T_{e}$	3
957943	(THA-$GalNAc_3$)o	$A_{es}{}^{m}C_{eo}G_{eo}G_{eo}{}^{m}C_{eo}A_{ds}T_{ds}T_{ds}G_{ds}G_{ds}T_{ds}G_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}A_{eo}G_{eo}T_{es}T_{es}T_{e}$	3

Subscripts: 'd' represents a 2'-deoxyribose sugar; 'e' represents a 2'-MOE modified sugar. All cytosine residues throughout each gapmer are 5-methyl cytosines, represented by a superscript 'm'. The internucleoside linkages are represented by subscript 'o' or 's', wherein 'o' represents a phosphodiester internucleoside linkage and 's' represents a phosphorothioate internucleoside linkage.

Treatment

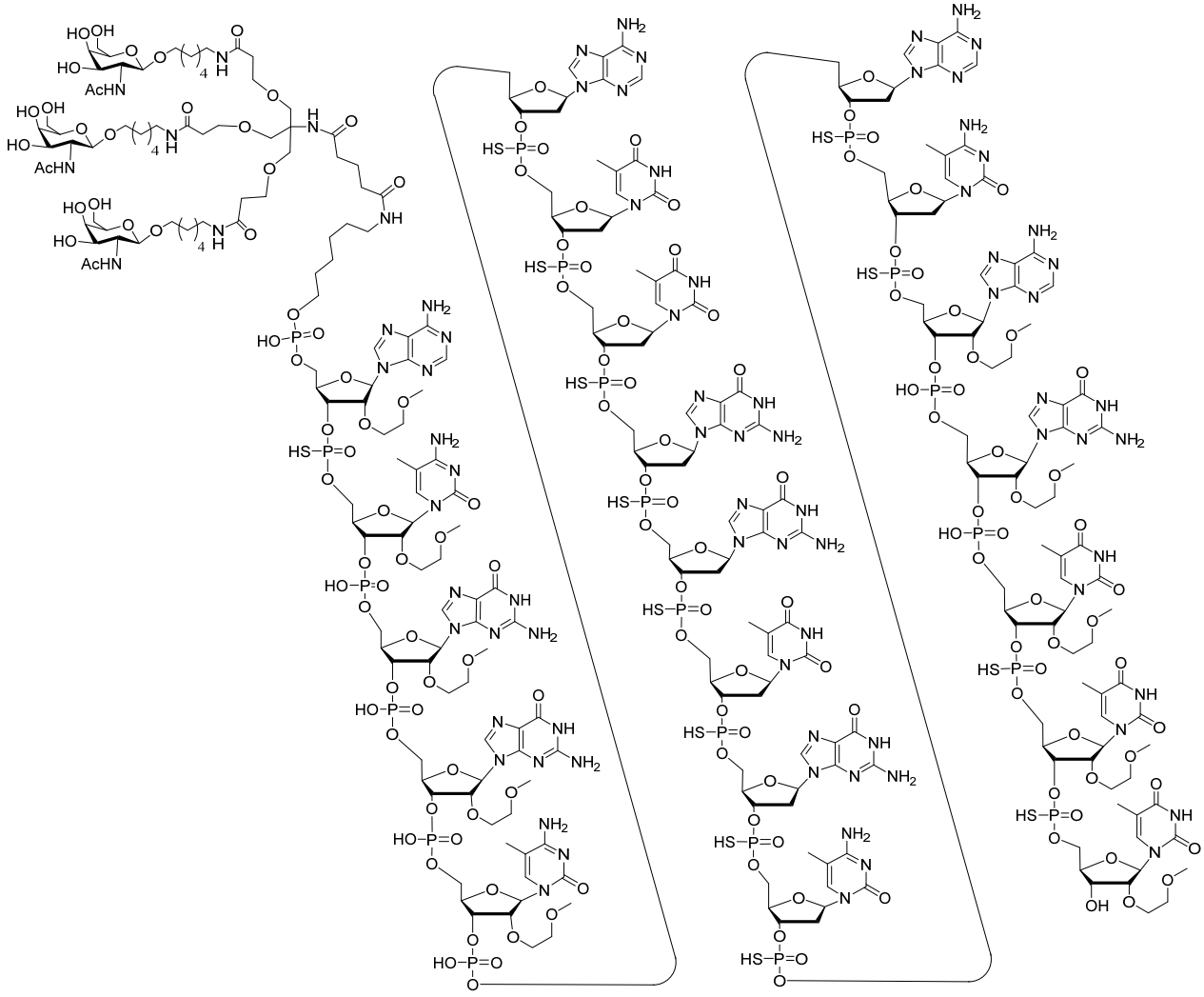
Transgenic hFXI mice were divided into groups of 8 mice each, 4 male and 4 female. Five groups of mice were administered 1.0, 2.5, 5.0, 10.0, or 25.0 mg/kg of Compound No. 416858. Five groups of mice were administered 0.1, 0.25, 0.50, 1.00, or 2.50 mg/kg of Compound No. 957943. Mice were administered oligomeric compounds twice a week for two weeks by subcutaneous injection and sacrificed at the end of the study. A group of 6 mice (3 male and 3 female) was administered PBS twice a week for two weeks and sacrificed at the end of the study. The PBS-injected group served as the control group to which oligomeric compound treated groups were compared.

RNA Analysis

After two weeks, mice were sacrificed and RNA was extracted from liver for real-time PCR analysis of measurement of RNA expression of human Factor XI using primer probe set RTS2965 (forward sequence ACGGTGTTTGCAGACAGCAA, designated herein as SEQ ID NO: 4; reverse sequence TGCAGATTCGGCCACAGA, designated herein as SEQ ID NO: 5; probe sequence ACAGTGTCATGGCTCCCGATGCTTTT, designated herein as SEQ ID NO: 6.). Results are presented as percent change of RNA, relative to PBS control, normalized to total RNA levels determined with Ribogreen®. Compound No. 416858 achieved an ED_{50} of 8.35 mg/kg and Compound No. 957943 achieved

CLAIMS

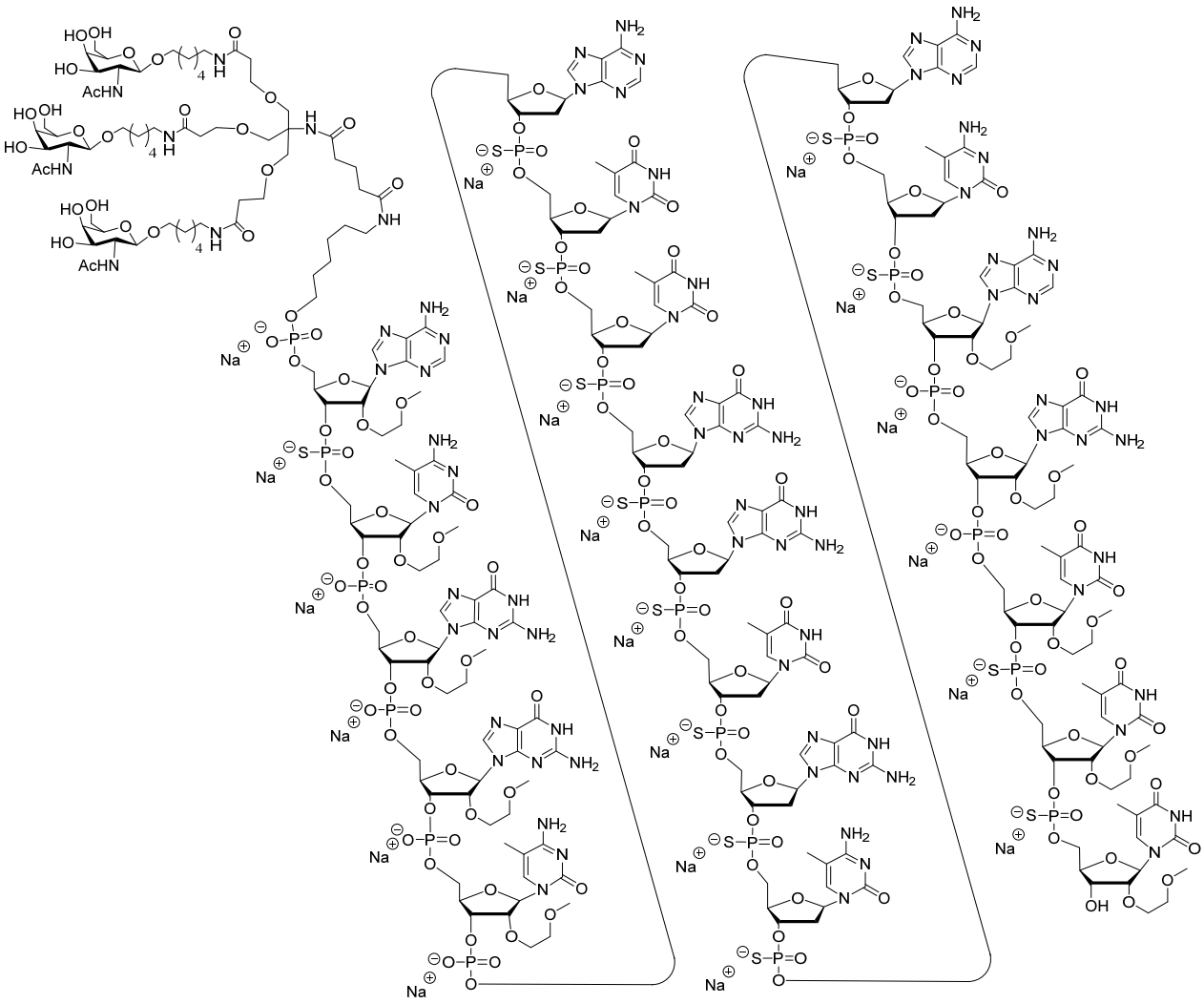
1. An oligomeric compound according to the following chemical structure:



(SEQ ID NO: 3)

or a salt thereof.

2. An oligomeric compound according to the following chemical structure:



(SEQ ID NO: 3).

3. An oligomeric compound comprising a modified oligonucleotide and a conjugate group according to the following formula:

(THA-GalNAc$_3$)o Aes mCeo Geo Geo mCeo Ads Tds Tds Gds Gds Tds Gds mCds Ads mCds Aeo Geo Tes Tes Te (SEQ ID NO: 3); wherein,

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

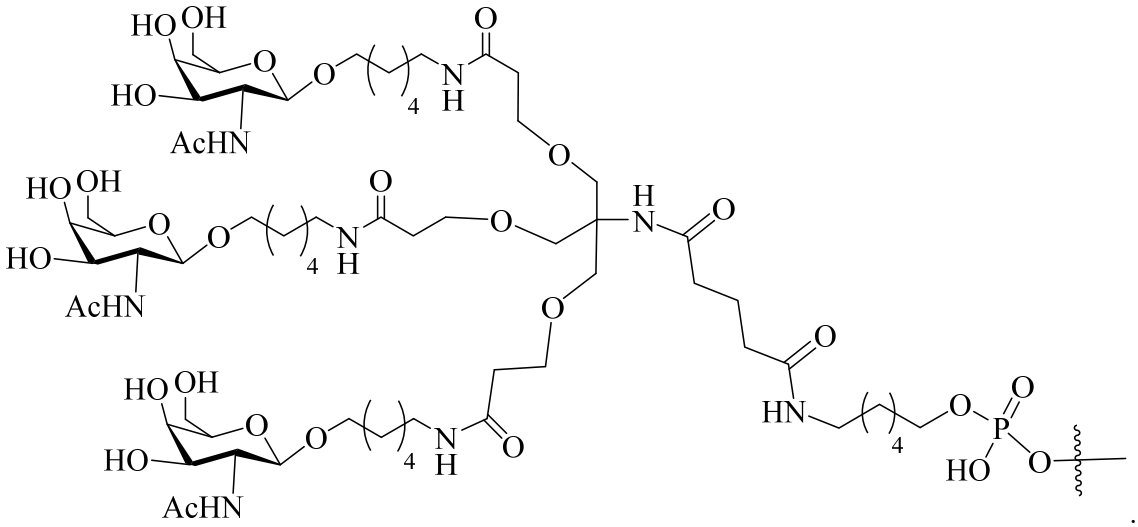
e = a 2'- $OCH_2CH_2OCH_3$ ribosyl sugar moiety,

d = a 2'- deoxyribosyl sugar moiety,

s = a phosphorothioate internucleoside linkage,

o = a phosphodiester internucleoside linkage, and

(THA-GalNAc$_3$)o =



4. The oligomeric compound of claim 1, which is the sodium salt or the potassium salt.

5. A population of oligomeric compounds of any one of claims 1-4, wherein all of the phosphorothioate internucleoside linkages are stereorandom.

6. A pharmaceutical composition comprising the oligomeric compound of any one of claims 1-4, or the population of oligomeric compounds of claim 5, and a pharmaceutically acceptable diluent.

7. The pharmaceutical composition of claim 6, wherein the pharmaceutically acceptable diluent is sterile saline or sterile water.

8. The pharmaceutical composition of claim 6, wherein the pharmaceutical composition consists of the oligomeric compound and sterile saline or sterile water.

9. The pharmaceutical composition of claim 6, wherein the pharmaceutical composition consists essentially of the oligomeric compound and sterile saline or sterile water.

10. Use of the oligomeric compound of any one of claims 1-4, the population of oligomeric compounds of claim 5, or the pharmaceutical composition of any one of claims 6-9 in the manufacture of a medicament for treating a thromboembolic condition.

11. Use of the oligomeric compound of any one of claims 1-4, the population of oligomeric compounds of claim 5, or the pharmaceutical composition of any one of claims 6-9 in the manufacture of a medicament for treating a disease selected from end stage renal disease (ESRD), chronic kidney disease (CKD), and coronary artery disease (CAD).

12. The oligomeric compound of any one of claims 1-4, the population of oligomeric compounds of claim 5, or the pharmaceutical composition of any one of claims 6-9, for use in therapy.