COMPOUNDS AND METHODS FOR REDUCING FXI EXPRESSION

Sequence Listing

The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled BIOL0337WOSEQ_ST25.txt, created on April 29, 2019, which is 40 KB in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety.

Field

Provided herein are compounds, methods, and pharmaceutical compositions for reducing an amount of Factor XI (FXI) RNA in a cell or animal, and in certain instances reducing the amount of FXI protein in a cell or animal. Such compounds, methods, and pharmaceutical compositions are useful to treat or prevent a thromboembolic condition. In certain embodiments, the compounds, methods, and pharmaceutical compositions are useful to treat or prevent a thromboembolic condition without increasing bleeding risk. Such thromboembolic conditions include deep vein thrombosis, venous or arterial thrombosis, pulmonary embolism, myocardial infarction, stroke, thrombosis associated with chronic kidney disease or end-stage renal disease (ESRD), including thrombosis associated with dialysis, or other procoagulant condition.

Background

The circulatory system requires mechanisms that prevent blood loss, as well as those that counteract inappropriate intravascular obstructions. Generally, coagulation comprises a cascade of reactions culminating in the conversion of soluble fibrinogen to an insoluble fibrin gel. The steps of the cascade involve the conversion of an inactive zymogen to an activated enzyme. The active enzyme then catalyzes the next step in the cascade.

Coagulation Cascade

The coagulation cascade may be initiated through two branches, the tissue factor pathway (also "extrinsic pathway"), which is the primary pathway, and the contact activation pathway (also "intrinsic pathway").

The tissue factor pathway is initiated by the cell surface receptor tissue factor (TF, also referred to as factor III), which is expressed constitutively by extravascular cells (pericytes, cardiomyocytes, smooth muscle cells, and keratinocytes) and expressed by vascular monocytes and endothelial cells upon induction by inflammatory cytokines or endotoxin. (Drake *et al*., *Am J Pathol* 1989, 134:1087-1097). TF is the high affinity cellular receptor for coagulation factor VIIa, a serine protease. In the absence of TF, VIIa has very low catalytic activity, and binding to TF is necessary to render VIIa functional through an allosteric mechanism. (Drake *et al*., *Am J Pathol* 1989, 134:1087-1097). The TF-VIIa complex activates factor X to

Xa. Xa in turn associates with its co-factor factor Va into a prothrombinase complex which in turn activates prothrombin, (also known as factor II or factor 2) to thrombin (also known as factor IIa, or factor 2a). Thrombin activates platelets, converts fibrinogen to fibrin and promotes fibrin cross-linking by activating factor XIII, thus forming a stable plug at sites where TF is exposed on extravascular cells. In addition, thrombin reinforces the coagulation cascade response by activating factors V and VIII.

The contact activation pathway is triggered by activation of factor XII to XIIa. Factor XIIa converts XI to XIa, and XIa converts IX to IXa. IXa associates with its cofactor VIIIa to convert X to Xa. The two pathways converge at this point as factor Xa associates with factor Va to activate prothrombin (factor II) to thrombin (factor IIa). Factor XI enhances both the formation and stability of clots *in vitro*, but is not thought to be involved in the initiation of clotting. Rather, Factor XI is important in the propagation phase of clot growth (von de Borne, et al., *Blood Coagulation and Fibrinolysis*, 2006, 17:251-257). Additionally, Factor XI-dependent amplification of thrombin formation leads to activation of TAFI (thrombin activatable fibrinolysis inhibitor), which renders clots less sensitive to fibrinolysis (Bouma et al, *J Thromb Haemost* 1999; 82: 1703-1708).

Inhibition of coagulation.

At least three mechanisms keep the coagulation cascade in check, namely the action of activated protein C, antithrombin, and tissue factor pathway inhibitor. Activated protein C is a serine protease that degrades cofactors Va and VIIIa. Protein C is activated by thrombin with thrombomodulin, and requires coenzyme Protein S to function. Antithrombin is a serine protease inhibitor (serpin) that inhibits serine proteases: thrombin, Xa, XIIa, XIa and IXa. Tissue factor pathway inhibitor inhibits the action of Xa and the TF-VIIa complex. (Schwartz AL et al., *Trends Cardiovasc Med.* 1997; 7:234 –239.)

Disease

Thrombosis is the pathological development of blood clots, and an embolism occurs when a blood clot migrates to another part of the body and interferes with organ function. Thromboembolism may cause conditions such as deep vein thrombosis, pulmonary embolism, myocardial infarction, and stroke. Significantly, thromboembolism is a major cause of morbidity affecting over 2 million Americans every year. (Adcock *et al*. *American Journal of Clinical Pathology*. 1997;108:434–49). While most cases of thrombosis are due to acquired extrinsic problems, for example, surgery, cancer, immobility, some cases are due to a genetic predisposition, for example, antiphospholipid syndrome and the autosomal dominant condition, Factor V Leiden. (Bertina RM *et al*. *Nature* 1994; 369:64-67.)

Treatment

The most commonly used anticoagulants, warfarin, heparin, low molecular weight heparin (LMWH), and newer direct oral anticoagulants (DOAC), all possess significant drawbacks.

Warfarin is typically used to treat patients suffering from atrial fibrillation. The drug interacts with vitamin K –dependent coagulation factors which include factors II, VII, IX and X. Anticoagulant proteins C and S are also inhibited by warfarin. Drug therapy using warfarin is further complicated by the fact that warfarin interacts with other medications, including drugs used to treat atrial fibrillation, such as amiodarone. Because therapy with warfarin is difficult to predict, patients must be carefully monitored in order to detect any signs of anomalous bleeding.

Heparin functions by activating antithrombin which inhibits both thrombin and factor X. (Bjork I, Lindahl U. *Mol Cell Biochem*. 1982 48: 161-182.) Treatment with heparin may cause an immunological reaction that makes platelets aggregate within blood vessels that can lead to thrombosis. This side effect is known as heparin-induced thrombocytopenia (HIT) resulting in increased bleeding and requires patient monitoring. Prolonged treatment with heparin may also lead to osteoporosis. LMWH can also inhibit Factor II, but to a lesser degree than unfractioned heparin (UFH). LMWH has been implicated in the development of HIT.

Several direct oral anticoagulants have been FDA-approved for the treatment of thrombotic disease, including four Factor Xa inhibitors Betrixaban, Apixaban, Rivaroxaban, and Edoxaban and one direct thrombin inhibitor, Dabigatran. (Smith, M., *Surg Clin N Am* 2018 98:219-238). Rivaroxaban, Dabigatran, and Edoxaban all exhibit increased bleeding, especially increased GI bleeding risk compared to warfarin.

Currently there remains a need for therapies to treat thromboembolic conditions without risk of increased bleeding. It is therefore an object herein to provide compounds, methods, and pharmaceutical compositions for the treatment of such diseases.

Brief Description of the Drawings

FIG. 1 shows pharmacodynamic results over time for single dose cohorts receiving Compound No. 957943, as measured by relative plasma FXI protein activity. **FIG. 1A** shows levels of plasma FXI protein activity. **FIG. 1B** shows percent change in plasma FXI protein activity relative to baseline.

FIG. 2 shows pharmacodynamic results over time for single dose cohorts receiving Compound No. 957943, as measured by ELISA. **FIG. 2A** shows concentrations of plasma FXI protein. **FIG. 2B** shows percent change in plasma FXI protein concentrations relative to baseline.

FIG. 3 shows pharmacodynamic results over time for multiple dose cohorts receiving Compound No. 957943, as measured by relative plasma FXI protein activity. **FIG. 3A** shows levels of plasma FXI protein activity. **FIG. 3B** shows percent change in plasma FXI protein activity relative to baseline.

FIG. 4 shows pharmacodynamic results over time for multiple dose cohorts receiving Compound No. 957943, as measured by ELISA. **FIG. 4A** shows concentrations of plasma FXI protein. **FIG. 4B** shows change in plasma FXI protein concentrations relative to baseline.

FIG. 5 shows pharmacodynamic results over time for multiple dose cohorts receiving 80 mg Compound No. 957943 every four weeks for thirteen weeks, as measured by relative plasma FXI protein

activity. **FIG. 5A** shows levels of plasma FXI protein activity. **FIG. 5B** shows mean percent change in plasma FXI protein activity.

FIG. 6 shows pharmacodynamic results over time for multiple dose cohorts receiving 80 mg Compound No. 957943 every four weeks for thirteen weeks, as measured by ELISA. **FIG. 6A** shows plasma FXI protein concentrations. **FIG. 6B** shows percent change in plasma FXI protein concentrations.

Summary of the Invention

Provided herein are compounds, methods and pharmaceutical compositions for reducing an amount of FXI RNA, and in certain embodiments reducing the amount of FXI protein in a cell or animal. In certain embodiments, methods and pharmaceutical compositions disclosed herein reduce FXI protein activity in the blood of an animal. In certain embodiments, the animal has or is at risk for a thromboembolic condition. In certain embodiments, the animal has or is at risk for deep vein thrombosis, venous or arterial thrombosis, pulmonary embolism, myocardial infarction, stroke, thrombosis associated with chronic kidney disease or end-stage renal disease (ESRD), including thrombosis associated with dialysis, or other procoagulant condition.

In certain embodiments, compounds useful for reducing a FXI RNA are oligomeric compounds. In certain embodiments, compounds useful for reducing a FXI RNA are modified oligonucleotides. In certain embodiments, compounds useful for reducing a FXI RNA are oligomeric compounds comprising a conjugate group and a modified oligonucleotide. In certain embodiments, compounds useful for reducing a FXI RNA are oligomeric compounds consisting of a conjugate group and a modified oligonucleotide.

Also provided are methods useful for treating, preventing, or ameliorating a thromboembolic condition. In certain embodiments, the thromboembolic condition is deep vein thrombosis, venous or arterial thrombosis, pulmonary embolism, myocardial infarction, stroke, thrombosis associated with chronic kidney disease or end-stage renal disease (ESRD), including thrombosis associated with dialysis, or other procoagulant condition.

Also provided are methods useful treating, preventing, or ameliorating a thromboembolic condition without increasing bleeding risk in an individual. In certain embodiments, the individual is at risk for a thromboembolic condition, including, but not limited to infarct, thrombosis, embolism, thromboembolism such as deep vein thrombosis, pulmonary embolism, myocardial infarction, and stroke. Such diseases, disorders, and conditions can have one or more risk factors, causes, or outcomes in common. Certain risk factors and causes for development of a thromboembolic condition include immobility, surgery (particularly orthopedic surgery), dialysis, malignancy, pregnancy, older age, use of oral contraceptives, atrial fibrillation, previous thromboembolic condition, chronic inflammatory disease, inherited or acquired prothrombotic clotting disorders and thrombosis associated with chronic kidney disease or end-stage renal disease (ESRD). Certain outcomes associated with development of a thromboembolic condition include decreased blood flow through an affected vessel, death of tissue, and death.

Detailed Description of the Invention

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive. Herein, the use of the singular includes the plural unless specifically stated otherwise. As used herein, the use of "or" means "and/or" unless stated otherwise. Furthermore, the use of the term "including" as well as other forms, such as "includes" and "included", is not limiting. Also, terms such as "element" or "component" encompass both elements and components comprising one unit and elements and components that comprise more than one subunit, unless specifically stated otherwise.

The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in this application, including, but not limited to, patents, patent applications, articles, books, and treatises, are hereby expressly incorporated-by-reference for the portions of the document discussed herein, as well as in their entirety.

Definitions

Unless specific definitions are provided, the nomenclature used in connection with, and the procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Where permitted, all patents, applications, published applications and other publications and other data referred to throughout in the disclosure are incorporated by reference herein in their entirety.

Unless otherwise indicated, the following terms have the following meanings:

DEFINITIONS

As used herein, "2'-deoxynucleoside" means a nucleoside comprising a 2'-H(H) deoxyribosyl sugar moiety, as found in naturally occurring deoxyribonucleic acids (DNA). In certain embodiments, a 2'-deoxynucleoside may comprise a modified nucleobase or may comprise an RNA nucleobase (uracil).

As used herein, "2'-substituted nucleoside" means a nucleoside comprising a 2'-substituted sugar moiety. As used herein, "2'-substituted" in reference to a sugar moiety means a sugar moiety comprising at least one 2'-substituent group other than H or OH.

As used herein, "5-methyl cytosine" means a cytosine modified with a methyl group attached to the 5 position. A 5-methyl cytosine is a modified nucleobase.

As used herein, "about" means plus or minus 7% of the provided value.

As used herein, "administering" means providing a pharmaceutical agent to an animal.

As used herein, "animal" means a human or non-human animal. In certain embodiments, the animal is a human.

As used herein, "antisense activity" means any detectable and/or measurable change attributable to the hybridization of an antisense compound to its target nucleic acid. In certain embodiments, antisense activity is a decrease in the amount or expression of a target nucleic acid or protein encoded by such target

nucleic acid compared to target nucleic acid levels or target protein levels in the absence of the antisense compound.

As used herein, "antisense compound" means an oligomeric compound capable of achieving at least one antisense activity.

As used herein, "cleavable moiety" means a bond or group of atoms that is cleaved under physiological conditions, for example, inside a cell or an animal.

As used herein, "complementary" in reference to an oligonucleotide means that at least 70% of the nucleobases of the oligonucleotide or one or more regions thereof and the nucleobases of another nucleic acid or one or more regions thereof are capable of hydrogen bonding with one another when the nucleobase sequence of the oligonucleotide and the other nucleic acid are aligned in opposing directions. Complementary nucleobases means nucleobases that are capable of forming hydrogen bonds with one another. Complementary nucleobase pairs include adenine (A) and thymine (T), adenine (A) and uracil (U), cytosine (C) and guanine (G), 5-methyl cytosine (mC) and guanine (G). Complementary oligonucleotides and/or nucleic acids need not have nucleobase complementarity at each nucleoside. Rather, some mismatches are tolerated. As used herein, "fully complementary" or "100% complementary" in reference to oligonucleotides means that oligonucleotides are complementary to another oligonucleotide or nucleic acid at each nucleoside of the oligonucleotide.

As used herein, "conjugate group" means a group of atoms that is directly attached to an oligonucleotide. Conjugate groups include a conjugate moiety and a conjugate linker that attaches the conjugate moiety to the oligonucleotide.

As used herein, "conjugate linker" means a single bond or group of atoms comprising at least one bond that connects a conjugate moiety to an oligonucleotide. In certain embodiments, a conjugate linker comprises a cleavable moiety.

As used herein, "conjugate moiety" means a group of atoms that is attached to an oligonucleotide via a conjugate linker. In certain embodiments, a conjugate moiety comprises a cell-targeting moiety.

As used herein, "contiguous" in the context of an oligonucleotide refers to nucleosides, nucleobases, sugar moieties, or internucleoside linkages that are immediately adjacent to each other. For example, "contiguous nucleobases" means nucleobases that are immediately adjacent to each other in a sequence.

As used herein, "chirally enriched population" means a plurality of molecules of identical molecular formula, wherein the number or percentage of molecules within the population that contain a particular stereochemical configuration at a particular chiral center is greater than the number or percentage of molecules expected to contain the same particular stereochemical configuration at the same particular chiral center within the population if the particular chiral center were stereorandom. Chirally enriched populations of molecules having multiple chiral centers within each molecule may contain one or more stereorandom chiral centers. In certain embodiments, the molecules are oligomeric compounds disclosed herein. In certain embodiments, the oligomeric compounds are antisense compounds. In certain embodiments, the molecules

are modified oligonucleotides. In certain embodiments, the molecules are oligomeric compounds comprising modified oligonucleotides.

As used herein, "dosage unit" means a formulation of an oligomeric compound, or pharmaceutical composition thereof, for administration, wherein the oligomeric compound is provided at a quantity of a single selected dose. The term dosage unit, as used herein, may comprise packaging or a container that contains the pharmaceutical composition, such as a vial or syringe. As used herein, "gapmer" means a modified oligonucleotide comprising an internal region having a plurality of nucleosides that support RNase H cleavage positioned between external regions having one or more nucleosides, wherein the nucleosides comprising the internal region are chemically distinct from the nucleoside or nucleosides comprising the external regions. The internal region may be referred to as the "gap" and the external regions may be referred to as the "wings." Unless otherwise indicated, "gapmer" refers to a sugar motif. Unless otherwise indicated, the sugar moieties of the nucleosides of the gap of a gapmer are unmodified 2'-deoxyribosyl. Thus, the term "MOE gapmer" indicates a gapmer having a sugar motif of 2'-MOE nucleosides in both wings and a gap of 2'-deoxynucleosides. Unless otherwise indicated, a MOE gapmer may comprise one or more modified internucleoside linkages and/or modified nucleobases and such modifications do not necessarily follow the gapmer pattern of the sugar modifications.

As used herein, "hybridization" means the pairing or annealing of complementary oligonucleotides and/or nucleic acids. While not limited to a particular mechanism, the most common mechanism of hybridization involves hydrogen bonding, which may be Watson-Crick, Hoogsteen or reversed Hoogsteen hydrogen bonding, between complementary nucleobases.

As used herein, "identifying an animal at risk for developing a thromboembolic condition" means identifying an animal having been diagnosed with a thromboembolic condition or identifying an animal predisposed to develop a thromboembolic condition. Individuals predisposed to develop a thromboembolic condition include those having one or more risk factors for thromboembolic conditions including immobility, surgery (particularly orthopedic surgery), dialysis, malignancy, pregnancy, older age, use of oral contraceptives, inherited or acquired prothrombotic clotting disorders, chronic kidney disease, and end-stage renal disease (ESRD). Such identification may be accomplished by any method including evaluating an individual's medical history and standard clinical tests or assessments.

As used herein, the term "internucleoside linkage" is the covalent linkage between adjacent nucleosides in an oligonucleotide. As used herein "modified internucleoside linkage" means any internucleoside linkage other than a phosphodiester internucleoside linkage. "Phosphorothioate internucleoside linkage" is a modified internucleoside linkage in which one of the non-bridging oxygen atoms of a phosphodiester internucleoside linkage is replaced with a sulfur atom.

As used herein, the term "linker region" in reference to a conjugate moiety refers that part of a conjugate linker that is not a cleavable moiety.

As used herein, “non-bicyclic modified sugar moiety” means a modified sugar moiety that comprises a modification, such as a substituent, that does not form a bridge between two atoms of the sugar to form a second ring.

As used herein, “mismatch” or “non-complementary” means a nucleobase of a first oligonucleotide that is not complementary with the corresponding nucleobase of a second oligonucleotide or target nucleic acid when the first and second oligonucleotide are aligned.

As used herein, “MOE” means methoxyethyl. ”2’-MOE” or “2’-MOE modified sugar” means a 2’-$OCH_2CH_2OCH_3$ group in place of the 2’-OH group of a ribosyl sugar moiety.

As used herein, “2’-MOE nucleoside” means a nucleoside comprising a 2’-MOE modified sugar.

As used herein, “monthly” means every 28 to 31 days.

As used herein, “motif” means the pattern of unmodified and/or modified sugar moieties, nucleobases, and/or internucleoside linkages, in an oligonucleotide.

As used herein, "nucleobase" means an unmodified nucleobase or a modified nucleobase. As used herein an “unmodified nucleobase” is adenine (A), thymine (T), cytosine (C), uracil (U), and guanine (G). As used herein, a “modified nucleobase” is a group of atoms other than unmodified A, T, C, U, or G capable of pairing with at least one unmodified nucleobase. A “5-methyl cytosine” is a modified nucleobase. A universal base is a modified nucleobase that can pair with any one of the five unmodified nucleobases. As used herein, “nucleobase sequence” means the order of contiguous nucleobases in a nucleic acid or oligonucleotide independent of any sugar or internucleoside linkage modification.

As used herein, “nucleoside” means a compound comprising a nucleobase and a sugar moiety. The nucleobase and sugar moiety are each, independently, unmodified or modified. As used herein, “modified nucleoside” means a nucleoside comprising a modified nucleobase and/or a modified sugar moiety. Modified nucleosides include abasic nucleosides, which lack a nucleobase. “Linked nucleosides” are nucleosides that are connected in a contiguous sequence (i.e., no additional nucleosides are presented between those that are linked).

As used herein, "oligomeric compound" means an oligonucleotide and optionally one or more additional features, such as a conjugate group or terminal group. An oligomeric compound may be paired with a second oligomeric compound that is complementary to the first oligomeric compound or may be unpaired. A “singled-stranded oligomeric compound” is an unpaired oligomeric compound. The term “oligomeric duplex” means a duplex formed by two oligomeric compounds having complementary nucleobase sequences. Each oligomeric compound of an oligomeric duplex may be referred to as a “duplexed oligomeric compound.”

As used herein, "oligonucleotide" means a strand of linked nucleosides connected via internucleoside linkages, wherein each nucleoside and internucleoside linkage may be modified or unmodified. Unless otherwise indicated, oligonucleotides consist of 8-50 linked nucleosides. As used herein, “modified oligonucleotide” means an oligonucleotide, wherein at least one nucleoside or internucleoside linkage is

modified. As used herein, "unmodified oligonucleotide" means an oligonucleotide that does not comprise any nucleoside modifications or internucleoside modifications.

As used herein, "pharmaceutically acceptable carrier or diluent" means any substance suitable for use in administering to an animal. Certain such carriers enable pharmaceutical compositions to be formulated as, for example, tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspension and lozenges for the oral ingestion by an animal. In certain embodiments, a pharmaceutically acceptable carrier or diluent is sterile water, distilled water for injection, sterile saline, sterile buffer solution or sterile artificial cerebrospinal fluid.

As used herein "pharmaceutically acceptable salts" means physiologically and pharmaceutically acceptable salts of compounds. Pharmaceutically acceptable salts retain the desired biological activity of the parent compound and do not impart undesired toxicological effects thereto.

As used herein "pharmaceutical composition" means a mixture of substances suitable for administering to an animal. For example, a pharmaceutical composition may comprise an oligomeric compound and a sterile aqueous solution. In certain embodiments, a pharmaceutical composition shows activity in free uptake assay in certain cell lines.

As used herein, "reducing or inhibiting the amount or activity" refers to a reduction or blockade of the transcriptional expression or activity relative to the transcriptional expression or activity in an untreated or control sample and does not necessarily indicate a total elimination of transcriptional expression or activity.

As used herein, "RNAi compound" means an antisense compound that acts, at least in part, through RISC or Ago2 to modulate a target nucleic acid and/or protein encoded by a target nucleic acid. RNAi compounds include, but are not limited to double-stranded siRNA, single-stranded RNA (ssRNA), and microRNA, including microRNA mimics. In certain embodiments, an RNAi compound modulates the amount, activity, and/or splicing of a target nucleic acid. The term RNAi compound excludes antisense compounds that act through RNase H.

As used herein, "self-complementary" in reference to an oligonucleotide means an oligonucleotide that at least partially hybridizes to itself.

As used herein, "stereorandom chiral center" in the context of a population of molecules of identical molecular formula means a chiral center having a random stereochemical configuration. For example, in a population of molecules comprising a stereorandom chiral center, the number of molecules having the (*S*) configuration of the stereorandom chiral center may be but is not necessarily the same as the number of molecules having the (*R*) configuration of the stereorandom chiral center. The stereochemical configuration of a chiral center is considered random when it is the results of a synthetic method that is not designed to control the stereochemical configuration. In certain embodiments, a stereorandom chiral center is a stereorandom phosphorothioate internucleoside linkage.

As used herein, "sugar moiety" means an unmodified sugar moiety or a modified sugar moiety. As used herein, "unmodified sugar moiety" means a 2'-OH(H) ribosyl moiety, as found in RNA (an "unmodified RNA sugar moiety"), or a 2'-H(H) deoxyribosyl moiety, as found in DNA (an "unmodified DNA sugar

moiety"). Unmodified sugar moieties have one hydrogen at each of the 1', 3', and 4' positions, an oxygen at the 3' position, and two hydrogens at the 5' position. As used herein, "modified sugar moiety" or "modified sugar" means a modified furanosyl sugar moiety or a sugar surrogate.

As used herein, "sugar surrogate" means a modified sugar moiety having other than a furanosyl moiety that can link a nucleobase to another group, such as an internucleoside linkage, conjugate group, or terminal group in an oligonucleotide. Modified nucleosides comprising sugar surrogates can be incorporated into one or more positions within an oligonucleotide and such oligonucleotides are capable of hybridizing to complementary oligomeric compounds or target nucleic acids.

As used herein, "thromboembolic condition" means any disease or condition involving an embolism caused by a thrombus. Examples of such diseases= and conditions include the categories of thrombosis, embolism, and thromboembolism. In certain embodiments, such diseases and conditions include deep vein thrombosis, venous or arterial thrombosis, pulmonary embolism, myocardial infarction, stroke, thrombosis associated with chronic kidney disease or end-stage renal disease (ESRD), including thrombosis associated with dialysis, or other procoagulant condition. Thromboembolic conditions may also be referred to as thromboembolic events or thrombotic events.

As used herein, "target nucleic acid" and "target RNA" mean a nucleic acid that an antisense compound is designed to affect.

As used herein, "target region" means a portion of a target nucleic acid to which an oligomeric compound is designed to hybridize.

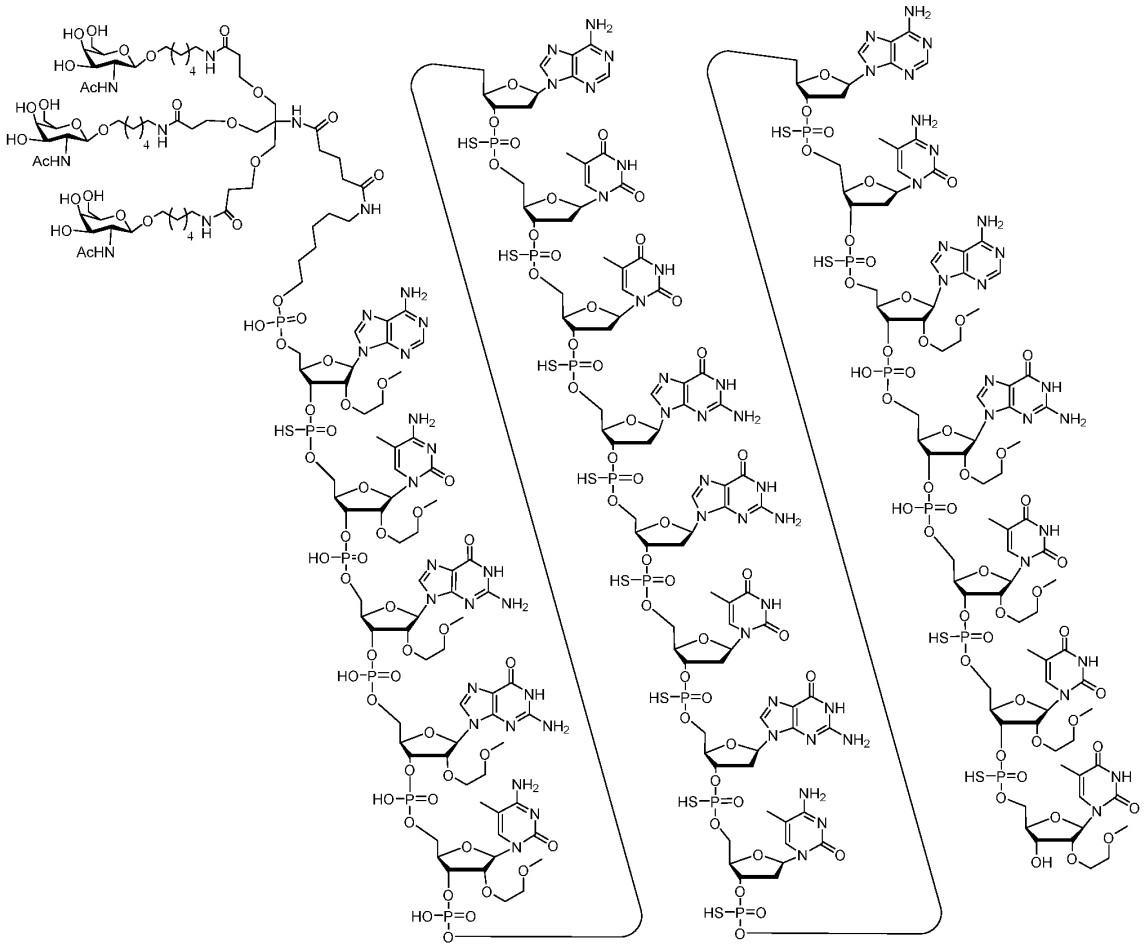
As used herein, "therapeutically effective amount" means an amount of a pharmaceutical agent that provides a therapeutic benefit to an animal. For example, a therapeutically effective amount of a pharmaceutical agent treats, prevents, or ameliorates a thromboembolic condition.

As used herein, "weekly" means every six to eight days.

CERTAIN EMBODIMENTS

The present disclosure provides the following non-limiting numbered embodiments:

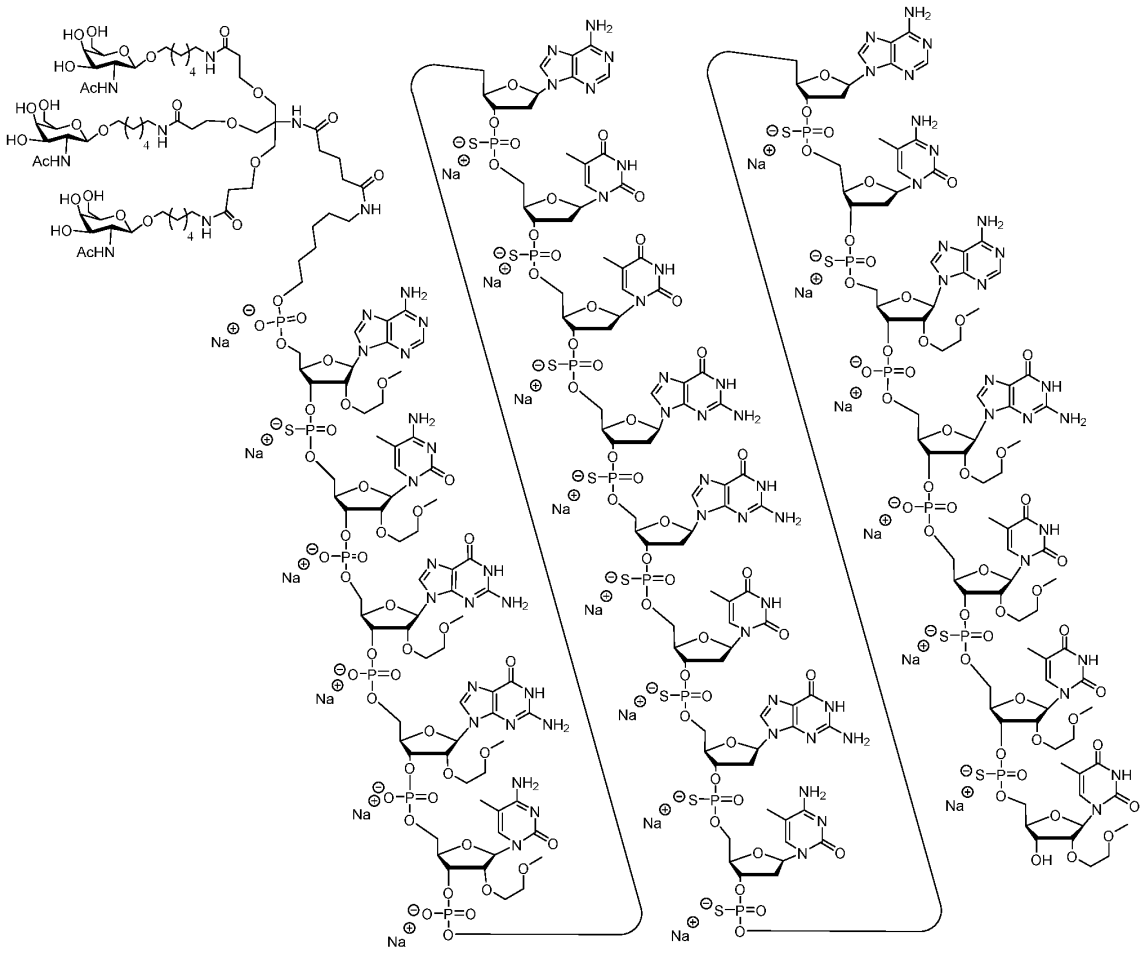
Embodiment 1. An oligomeric compound according to the following formula:



(SEQ ID NO: 3)

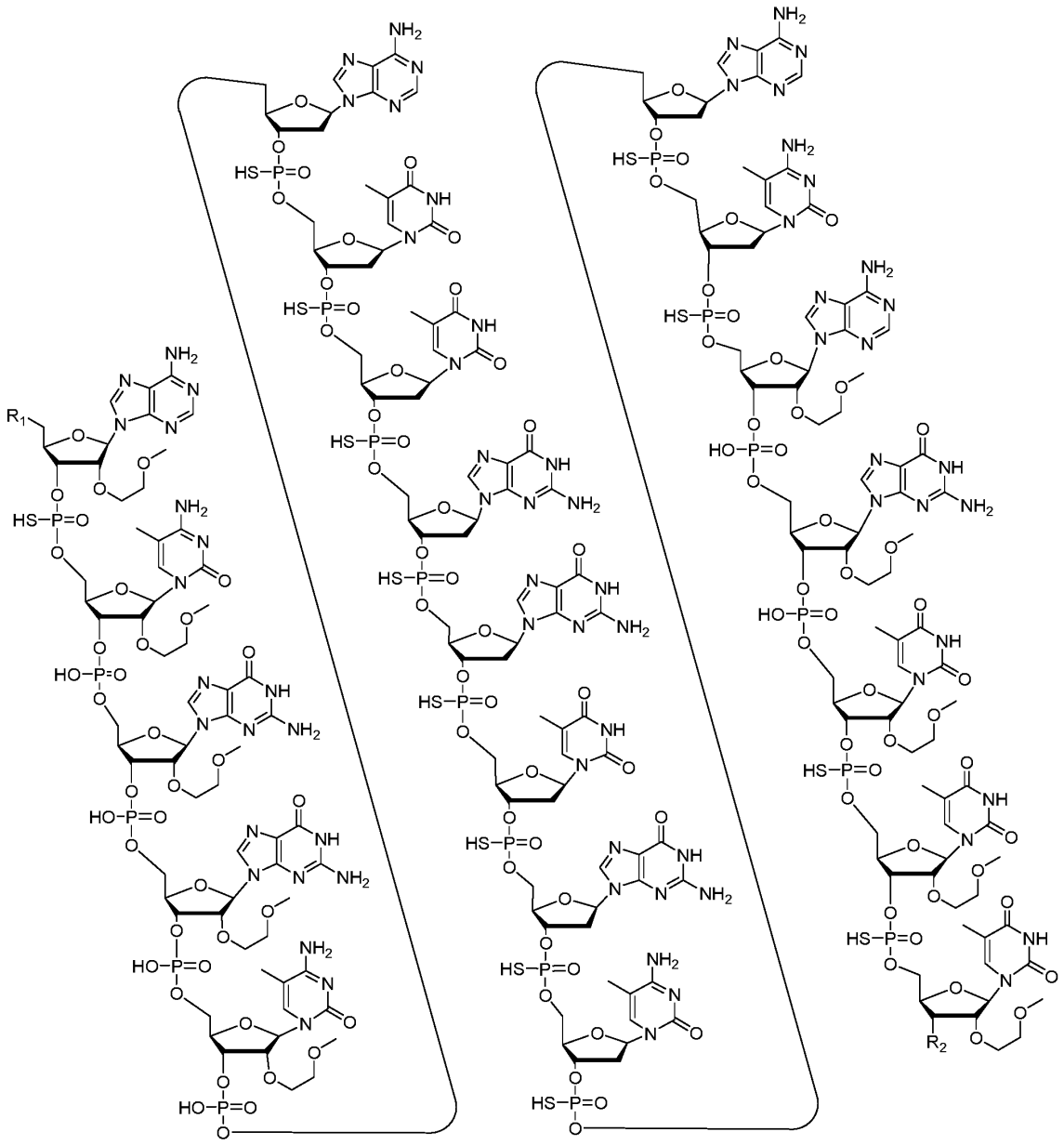
or a salt thereof.

Embodiment 2. An oligomeric compound according to the following formula:



(SEQ ID NO: 3).

Embodiment 3. An oligomeric compound comprising a modified oligonucleotide according to the following formula:



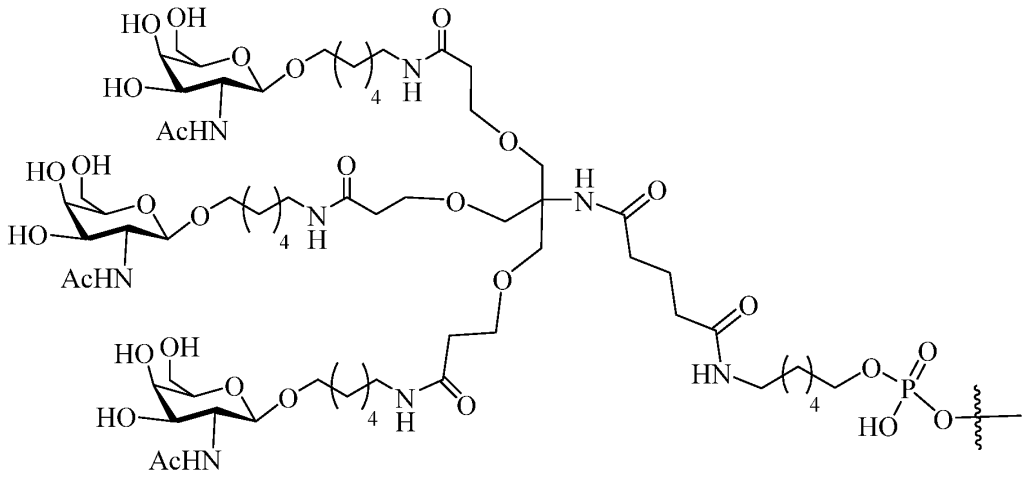
(SEQ ID NO:3);

wherein one of R_1 or R_2 is a conjugate group comprising at least one, two, or three GalNAc ligands, and the other of R_1 or R_2 is -OH;

or a salt thereof.

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'- MOE modified sugar,

d = a 2'-deoxyribose sugar,

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.

Embodiment 8. The chirally enriched population of embodiment 6 or 7, wherein the population is enriched for oligomeric compounds having a modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the (Rp) configuration.

Embodiment 9. The chirally enriched population of embodiment 6, wherein the population is enriched for oligomeric compounds having a modified oligonucleotide having a particular, independently selected stereochemical configuration at each phosphorothioate internucleoside linkage.

Embodiment 10. The chirally enriched population of embodiment 9, wherein the population is enriched for oligomeric compounds having a modified oligonucleotide having the (*Sp*) configuration at each phosphorothioate internucleoside linkage.

Embodiment 11. The chirally enriched population of embodiment 9, wherein the population is enriched for oligomeric compounds having a modified oligonucleotide having the (*Rp*) configuration at each phosphorothioate internucleoside linkage.

Embodiment 12. The chirally enriched population of embodiment 6 or 9 wherein the population is enriched for oligomeric compounds having a modified oligonucleotide having at least 3 contiguous phosphorothioate internucleoside linkages in the *Sp*-*Sp*-*Rp* configurations, in the 5' to 3' direction.

Embodiment 13. A population of oligomeric compounds having a modified oligonucleotide of any of embodiments 1-5, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.

Embodiment 14. A pharmaceutical composition comprising the oligomeric compound of any one of embodiments 1-5, the chirally enriched population of any one of embodiments 6-12, or the population of embodiment 13, and a pharmaceutically acceptable carrier or diluent.

Embodiment 15. The pharmaceutical composition of embodiment 14, wherein the pharmaceutically acceptable diluent is phosphate buffered saline.

Embodiment 16. The pharmaceutical composition of embodiment 14, wherein the pharmaceutical composition consists or consists essentially of the oligomeric compound and phosphate buffered saline.

Embodiment 17. The pharmaceutical composition of any one of embodiments 14-16, wherein the concentration of the oligomeric compound in the pharmaceutically acceptable carrier or diluent is selected from:

a) 5 mg/ml, 10 mg/ml, 15 mg/ml, 20 mg/ml, 25 mg/ml, 30 mg/ml, 35 mg/ml, 40 mg/ml, 45 mg/ml, 50 mg/ml, 55 mg/ml, 60 mg/ml, 65 mg/ml, 70 mg/ml, 75 mg/ml, 80 mg/ml, 85 mg/ml, 90 mg/ml, 95 mg/ml, 100 mg/ml, 105 mg/ml, 110 mg/ml, 115 mg/ml, 120 mg/ml, 125 mg/ml, 130 mg/ml, 135 mg/ml, 140 mg/ml, 145 mg/ml, 150 mg/ml, 155 mg/ml, 160 mg/ml;

b) about 5 mg/ml, about 10 mg/ml, about 15 mg/ml, about 20 mg/ml, about 25 mg/ml, about 30 mg/ml, about 35 mg/ml, about 40 mg/ml, about 45 mg/ml, about 50 mg/ml, about 55 mg/ml, about 60 mg/ml, about 65 mg/ml, about 70 mg/ml, about 75 mg/ml, about 80 mg/ml, about 85 mg/ml, about 90 mg/ml, about 95 mg/ml, about 100 mg/ml, about 105 mg/ml, about 110 mg/ml, about 115 mg/ml, about

120 mg/ml, about 125 mg/ml, about 130 mg/ml, about 135 mg/ml, about 140 mg/ml, about 145 mg/ml, about 150 mg/ml, about 155 mg/ml, about 160 mg/ml; and

c) 20 mg/ml, 21 mg/ml, 22 mg/ml, 23 mg/ml, 24 mg/ml, 25 mg/ml, 26 mg/ml, 27 mg/ml, 28 mg/ml, 29 mg/ml, 30 mg/ml, 31 mg/ml, 32 mg/ml, 33 mg/ml, 34 mg/ml, 35 mg/ml, 36 mg/ml, 37 mg/ml, 38 mg/ml, 39 mg/ml, 40 mg/ml, 41 mg/ml, 42 mg/ml, 43 mg/ml, 44 mg/ml, 45 mg/ml, 46 mg/ml, 47 mg/ml, 48 mg/ml, 49 mg/ml, 50 mg/ml, 51 mg/ml, 52 mg/ml, 53 mg/ml, 54 mg/ml, 55 mg/ml, 56 mg/ml, 57 mg/ml, 58 mg/ml, 59 mg/ml, 60 mg/ml, 61 mg/ml, 62 mg/ml, 63 mg/ml, 64 mg/ml, 65 mg/ml, 66 mg/ml, 67 mg/ml, 68 mg/ml, 69 mg/ml, 70 mg/ml, 71 mg/ml, 72 mg/ml, 73 mg/ml, 74 mg/ml, 75 mg/ml, 76 mg/ml, 77 mg/ml, 78 mg/ml, 79 mg/ml, 80 mg/ml, 81 mg/ml, 82 mg/ml, 83 mg/ml, 84 mg/ml, 85 mg/ml, 86 mg/ml, 87 mg/ml, 88 mg/ml, 89 mg/ml, 90 mg/ml, 91 mg/ml, 92 mg/ml, 93 mg/ml, 94 mg/ml, 95 mg/ml, 96 mg/ml, 97 mg/ml, 98 mg/ml, 99 mg/ml, 100 mg/ml, 101 mg/ml, 102 mg/ml, 103 mg/ml, 104 mg/ml, 105 mg/ml, 106 mg/ml, 107 mg/ml, 108 mg/ml, 109 mg/ml, 110 mg/ml, 111 mg/ml, 112 mg/ml, 113 mg/ml, 114 mg/ml, 115 mg/ml, 116 mg/ml, 117 mg/ml, 118 mg/ml, 119 mg/ml, 120 mg/ml, 121 mg/ml, 122 mg/ml, 123 mg/ml, 124 mg/ml, 125 mg/ml, 126 mg/ml, 127 mg/ml, 128 mg/ml, 129 mg/ml, 130 mg/ml, 131 mg/ml, 132 mg/ml, 133 mg/ml, 134 mg/ml, 135 mg/ml, 136 mg/ml, 137 mg/ml, 138 mg/ml, 139 mg/ml, 140 mg/ml;

d) about 20 mg/ml, about 21 mg/ml, about 22 mg/ml, about 23 mg/ml, about 24 mg/ml, about 25 mg/ml, about 26 mg/ml, about 27 mg/ml, about 28 mg/ml, about 29 mg/ml, about 30 mg/ml, about 31 mg/ml, about 32 mg/ml, about 33 mg/ml, about 34 mg/ml, about 35 mg/ml, about 36 mg/ml, about 37 mg/ml, about 38 mg/ml, about 39 mg/ml, about 40 mg/ml, about 41 mg/ml, about 42 mg/ml, about 43 mg/ml, about 44 mg/ml, about 45 mg/ml, about 46 mg/ml, about 47 mg/ml, about 48 mg/ml, about 49 mg/ml, about 50 mg/ml, about 51 mg/ml, about 52 mg/ml, about 53 mg/ml, about 54 mg/ml, about 55 mg/ml, about 56 mg/ml, about 57 mg/ml, about 58 mg/ml, about 59 mg/ml, about 60 mg/ml, about 61 mg/ml, about 62 mg/ml, about 63 mg/ml, about 64 mg/ml, about 65 mg/ml, about 66 mg/ml, about 67 mg/ml, about 68 mg/ml, about 69 mg/ml, about 70 mg/ml, about 71 mg/ml, about 72 mg/ml, about 73 mg/ml, about 74 mg/ml, about 75 mg/ml, about 76 mg/ml, about 77 mg/ml, about 78 mg/ml, about 79 mg/ml, about 80 mg/ml, about 81 mg/ml, about 82 mg/ml, about 83 mg/ml, about 84 mg/ml, about 85 mg/ml, about 86 mg/ml, about 87 mg/ml, about 88 mg/ml, about 89 mg/ml, about 90 mg/ml, about 91 mg/ml, about 92 mg/ml, about 93 mg/ml, about 94 mg/ml, about 95 mg/ml, about 96 mg/ml, about 97 mg/ml, about 98 mg/ml, about 99 mg/ml, about 100 mg/ml, about 101 mg/ml, about 102 mg/ml, about 103 mg/ml, about 104 mg/ml, about 105 mg/ml, about 106 mg/ml, about 107 mg/ml, about 108 mg/ml, about 109 mg/ml, about 110 mg/ml, about 111 mg/ml, about 112 mg/ml, about 113 mg/ml, about 114 mg/ml, about 115 mg/ml, about 116 mg/ml, about 117 mg/ml, about 118 mg/ml, about 119 mg/ml, about 120 mg/ml, about 121 mg/ml, about 122 mg/ml, about 123 mg/ml, about 124 mg/ml, about 125 mg/ml, about 126 mg/ml, about 127 mg/ml, about 128 mg/ml, about 129 mg/ml, about 130 mg/ml, about 131

mg/ml, about 132 mg/ml, about 133 mg/ml, about 134 mg/ml, about 135 mg/ml, about 136 mg/ml, about 137 mg/ml, about 138 mg/ml, about 139 mg/ml, and about 140 mg/ml.

Embodiment 18. The pharmaceutical composition of any one of embodiments 14-16, wherein the concentration of the oligomeric compound in the pharmaceutically acceptable carrier or diluent is selected from 20 mg/ml to 180 mg/ml, 20 mg/ml to 170 mg, 20 mg/ml to 160 mg/ml, 20 mg/ml to 150 mg/ml, 20 mg/ml to 140 mg/ml, 20 mg/ml to 130 mg/ml, 20 mg/ml to 120 mg/ml, 20 mg/ml to 110 mg/ml, 20 mg/ml to 100 mg/ml, 20 mg/ml to 90 mg/ml, 20 mg/ml to 80 mg/ml, 20 mg/ml to 70 mg/ml, 20 mg/ml to 60 mg/ml, 20 mg/ml to 50 mg/ml, 20 mg/ml to 40 mg/ml, 20 mg/ml to 30 mg/ml, 30 mg/ml to 180 mg/ml, 30 mg/ml to 170 mg, 30 mg/ml to 160 mg/ml, 30 mg/ml to 150 mg/ml, 30 mg/ml to 140 mg/ml, 30 mg/ml to 130 mg/ml, 30 mg/ml to 120 mg/ml, 30 mg/ml to 110 mg/ml, 30 mg/ml to 100 mg/ml, 30 mg/ml to 90 mg/ml, 30 mg/ml to 80 mg/ml, 30 mg/ml to 70 mg/ml, 30 mg/ml to 60 mg/ml, 30 mg/ml to 50 mg/ml, 30 mg/ml to 40 mg/ml, 40 mg/ml to 180 mg/ml, 40 mg/ml to 170 mg, 40 mg/ml to 160 mg/ml, 40 mg/ml to 150 mg/ml, 40 mg/ml to 140 mg/ml, 40 mg/ml to 130 mg/ml, 40 mg/ml to 120 mg/ml, 40 mg/ml to 110 mg/ml, 40 mg/ml to 100 mg/ml, 40 mg/ml to 90 mg/ml, 40 mg/ml to 80 mg/ml, 40 mg/ml to 70 mg/ml, 40 mg/ml to 60 mg/ml, 40 mg/ml to 50 mg/ml, 50 mg/ml to 180 mg/ml, 50 mg/ml to 170 mg, 50 mg/ml to 160 mg/ml, 50 mg/ml to 150 mg/ml, 50 mg/ml to 140 mg/ml, 50 mg/ml to 130 mg/ml, 50 mg/ml to 120 mg/ml, 50 mg/ml to 110 mg/ml, 50 mg/ml to 100 mg/ml, 50 mg/ml to 90 mg/ml, 50 mg/ml to 80 mg/ml, 50 mg/ml to 70 mg/ml, 50 mg/ml to 60 mg/ml, 60 mg/ml to 180 mg/ml, 60 mg/ml to 170 mg, 60 mg/ml to 160 mg/ml, 60 mg/ml to 150 mg/ml, 60 mg/ml to 140 mg/ml, 60 mg/ml to 130 mg/ml, 60 mg/ml to 120 mg/ml, 60 mg/ml to 110 mg/ml, 60 mg/ml to 100 mg/ml, 60 mg/ml to 90 mg/ml, 60 mg/ml to 80 mg/ml, 60 mg/ml to 70 mg/ml, 70 mg/ml to 180 mg/ml, 70 mg/ml to 170 mg, 70 mg/ml to 160 mg/ml, 70 mg/ml to 150 mg/ml, 70 mg/ml to 140 mg/ml, 70 mg/ml to 130 mg/ml, 70 mg/ml to 120 mg/ml, 70 mg/ml to 110 mg/ml, 70 mg/ml to 100 mg/ml, 70 mg/ml to 90 mg/ml, 70 mg/ml to 80 mg/ml, 80 mg/ml to 180 mg/ml, 80 mg/ml to 170 mg, 80 mg/ml to 160 mg/ml, 80 mg/ml to 150 mg/ml, 80 mg/ml to 140 mg/ml, 80 mg/ml to 130 mg/ml, 80 mg/ml to 120 mg/ml, 80 mg/ml to 110 mg/ml, 80 mg/ml to 100 mg/ml, 80 mg/ml to 90 mg/ml, 90 mg/ml to 180 mg/ml, 90 mg/ml to 170 mg, 90 mg/ml to 160 mg/ml, 90 mg/ml to 150 mg/ml, 90 mg/ml to 140 mg/ml, 90 mg/ml to 130 mg/ml, 90 mg/ml to 120 mg/ml, 90 mg/ml to 110 mg/ml, 90 mg/ml to 100 mg/ml, 100 mg/ml to 180 mg/ml, 100 mg/ml to 170 mg, 100 mg/ml to 160 mg/ml, 100 mg/ml to 150 mg/ml, 100 mg/ml to 140 mg/ml, 100 mg/ml to 130 mg/ml, 100 mg/ml to 120 mg/ml, 100 mg/ml to 110 mg/ml, 110 mg/ml to 180 mg/ml, 110 mg/ml to 170 mg, 110 mg/ml to 160 mg/ml, 110 mg/ml to 150 mg/ml, 110 mg/ml to 140 mg/ml, 110 mg/ml to 130 mg/ml, 110 mg/ml to 120 mg/ml, 120 mg/ml to 180 mg/ml, 120 mg/ml to 170 mg, 120 mg/ml to 160 mg/ml, 120 mg/ml to 150 mg/ml, 120 mg/ml to 140 mg/ml, 120 mg/ml to 130 mg/ml, 130 mg/ml to 180 mg/ml, 130 mg/ml to 170 mg, 130 mg/ml to 160 mg/ml, 130 mg/ml to 150 mg/ml, 130 mg/ml to 140 mg/ml, 140 mg/ml to 180 mg/ml, 140 mg/ml to 170 mg/ml, 140 mg/ml to 160 mg/ml, 140 mg/ml to 150 mg/ml, 150 mg/ml to 180 mg/ml, 150 mg/ml to 170 mg/ml, 150 mg/ml to 160 mg/ml, 160 mg/ml to 180 mg/ml, 160 mg/ml to 170 mg/ml, and 170 mg/ml to 180 mg/ml.

Embodiment 19. The pharmaceutical composition of any one of embodiments 14-18, wherein the pharmaceutical composition is in a form of a dosage unit.

Embodiment 20. The pharmaceutical composition of embodiment 19, wherein the oligomeric compound is present in the dosage unit at an amount selected from:

a) 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 105 mg, 110 mg, 115 mg, 120 mg, 125 mg, 130 mg, 135 mg, 140 mg, 145 mg, 150 mg, 155 mg, 160 mg, 165 mg, 170 mg, 175 mg, 180 mg, 185 mg, 190 mg, 195 mg, 200 mg, 205 mg, 210 mg, 215 mg, 220 mg, 225 mg, 230 mg, 235 mg, 240 mg, 245 mg, 250 mg, 255 mg, 260 mg, 265 mg, 270 mg, 275 mg, 280 mg, 285 mg, 290 mg, 295 mg, 300 mg;

b) about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg;

c) 20 mg, 21 mg, 22 mg, 23 mg, 24 mg, 25 mg, 26 mg, 27 mg, 28 mg, 29 mg, 30 mg, 31 mg, 32 mg, 33 mg, 34 mg, 35 mg, 36 mg, 37 mg, 38 mg, 39 mg, 40 mg, 41 mg, 42 mg, 43 mg, 44 mg, 45 mg, 46 mg, 47 mg, 48 mg, 49 mg, 50 mg, 51 mg, 52 mg, 53 mg, 54 mg, 55 mg, 56 mg, 57 mg, 58 mg, 59 mg, 60 mg, 61 mg, 62 mg, 63 mg, 64 mg, 65 mg, 66 mg, 67 mg, 68 mg, 69 mg, 70 mg, 71 mg, 72 mg, 73 mg, 74 mg, 75 mg, 76 mg, 77 mg, 78 mg, 79 mg, 80 mg, 81 mg, 82 mg, 83 mg, 84 mg, 85 mg, 86 mg, 87 mg, 88 mg, 89 mg, 90 mg, 91 mg, 92 mg, 93 mg, 94 mg, 95 mg, 96 mg, 97 mg, 98 mg, 99 mg, 100 mg, 101 mg, 102 mg, 103 mg, 104 mg, 105 mg, 106 mg, 107 mg, 108 mg, 109 mg, 110 mg, 111 mg, 112 mg, 113 mg, 114 mg, 115 mg, 116 mg, 117 mg, 118 mg, 119 mg, 120 mg, 121 mg, 122 mg, 123 mg, 124 mg, 125 mg, 126 mg, 127 mg, 128 mg, 129 mg, 130 mg, 131 mg, 132 mg, 133 mg, 134 mg, 135 mg, 136 mg, 137 mg, 138 mg, 139 mg, 140 mg;

d) about 20 mg, about 21 mg, about 22 mg, about 23 mg, about 24 mg, about 25 mg, about 26 mg, about 27 mg, about 28 mg, about 29 mg, about 30 mg, about 31 mg, about 32 mg, about 33 mg, about 34 mg, about 35 mg, about 36 mg, about 37 mg, about 38 mg, about 39 mg, about 40 mg, about 41 mg, about 42 mg, about 43 mg, about 44 mg, about 45 mg, about 46 mg, about 47 mg, about 48 mg, about 49 mg, about 50 mg, about 51 mg, about 52 mg, about 53 mg, about 54 mg, about 55 mg, about 56 mg, about 57 mg, about 58 mg, about 59 mg, about 60 mg, about 61 mg, about 62 mg, about 63 mg, about 64 mg, about 65 mg, about 66 mg, about 67 mg, about 68 mg, about 69 mg, about 70 mg, about 71 mg, about 72 mg, about 73 mg, about 74 mg, about 75 mg, about 76 mg, about 77 mg, about 78 mg, about 79

mg, about 80 mg, about 81 mg, about 82 mg, about 83 mg, about 84 mg, about 85 mg, about 86 mg, about 87 mg, about 88 mg, about 89 mg, about 90 mg, about 91 mg, about 92 mg, about 93 mg, about 94 mg, about 95 mg, about 96 mg, about 97 mg, about 98 mg, about 99 mg, about 100 mg, about 101 mg, about 102 mg, about 103 mg, about 104 mg, about 105 mg, about 106 mg, about 107 mg, about 108 mg, about 109 mg, about 110 mg, about 111 mg, about 112 mg, about 113 mg, about 114 mg, about 115 mg, about 116 mg, about 117 mg, about 118 mg, about 119 mg, about 120 mg, about 121 mg, about 122 mg, about 123 mg, about 124 mg, about 125 mg, about 126 mg, about 127 mg, about 128 mg, about 129 mg, about 130 mg, about 131 mg, about 132 mg, about 133 mg, about 134 mg, about 135 mg, about 136 mg, about 137 mg, about 138 mg, about 139 mg, about 140 mg;

e) 75.0 mg, 75.1 mg, 75.2 mg, 75.3 mg, 75.4 mg, 75.5 mg, 75.6 mg, 75.7 mg, 75.8 mg, 75.9 mg, 76.0 mg, 76.1 mg, 76.2 mg, 76.3 mg. 76.4 mg, 76.5 mg, 76.6 mg, 76.7 mg, 76.8 mg, 76.9 mg, 77.0 mg, 77.1 mg, 77.2 mg, 77.3 mg, 77.4 mg, 77.5 mg, 77.6 mg, 77.7 mg, 77.8 mg, 77.9 mg, 78.0 mg, 78.1 mg, 78.2 mg, 78.3 mg. 78.4 mg, 78.5 mg, 78.6 mg, 78.7 mg, 78.8 mg, 78.9 mg, 79.0 mg, 79.1 mg, 79.2 mg, 79.3 mg, 79.4 mg, 79.5 mg, 79.6 mg, 79.7 mg, 79.8 mg, 79.9 mg, 80.0 mg, 80.1 mg, 80.2 mg, 80.3 mg. 80.4 mg, 80.5 mg, 80.6 mg, 80.7 mg, 80.8 mg, 80.9 mg, 81.0 mg, 81.1 mg, 81.2 mg, 81.3 mg, 81.4 mg, 81.5 mg, 81.6 mg, 81.7 mg, 81.8 mg, 81.9 mg, 82.0 mg, 82.1 mg, 82.2 mg, 82.3 mg. 82.4 mg, 82.5 mg, 82.6 mg, 82.7 mg, 82.8 mg, 82.9 mg, 83.0 mg, 83.1 mg, 83.2 mg, 83.3 mg, 83.4 mg, 83.5 mg, 83.6 mg, 83.7 mg, 83.8 mg, 83.9 mg, 84.0 mg, 84.1 mg, 84.2 mg, 84.3 mg. 84.4 mg, 84.5 mg, 84.6 mg, 84.7 mg, 84.8 mg, 84.9 mg, 85.0 mg; and

f) about 75.0 mg, about 75.1 mg, about 75.2 mg, about 75.3 mg, about 75.4 mg, about 75.5 mg, about 75.6 mg, about 75.7 mg, about 75.8 mg, about 75.9 mg, about 76.0 mg, about 76.1 mg, about 76.2 mg, about 76.3 mg. about about 76.4 mg, about 76.5 mg, about 76.6 mg, about 76.6 about 76.7 mg, about 76.8 mg, about 76.9 mg, about 77.0 mg, about 77.1 mg, about 77.2 mg, about 77.3 mg, about 77.4 mg, about 77.5 mg, about 77.6 mg, about 77.7 mg, about 77.8 mg, about 77.9 mg, about 78.0 mg, about 78.1 mg, about 78.2 mg, about 78.3 mg. about 78.4 mg, about 78.5 mg, about 78.6 mg, about 78.7 mg, about 78.8 mg, about 78.9 mg, about 79.0 mg, about 79.1 mg, about 79.2 mg, about 79.3 mg, about 79.4 mg, about 79.5 mg, about 79.6 mg, about 79.7 mg, about 79.8 mg, about 79.9 mg, about 80.0 mg, about 80.1 mg, about 80.2 mg, about 80.3 mg. about 80.4 mg, about 80.5 mg, about 80.6 mg, about 80.7 mg, about 80.8 mg, about 80.9 mg, about 81.0 mg, about 81.1 mg, about 81.2 mg, about 81.3 mg, about 81.4 mg, about 81.5 mg, about 81.6 mg, about 81.7 mg, about 81.8 mg, about 81.9 mg, about 82.0 mg, about 82.1 mg, about 82.2 mg, about 82.3 mg. about 82.4 mg, about 82.5 mg, about 82.6 mg, about 82.7 mg, about 82.8 mg, about 82.9 mg, about 83.0 mg, about 83.1 mg, about 83.2 mg, about 83.3 mg, about 83.4 mg, about 83.5 mg, about 83.6 mg, about 83.7 mg, about 83.8 mg, about 83.9 mg, about 84.0 mg, about 84.1 mg, about 84.2 mg, about 84.3 mg. about 84.4 mg, about 84.5 mg, about 84.6 mg, about 84.7 mg, about 84.8 mg, about 84.9 mg, and about 85.0 mg.

Embodiment 21. The pharmaceutical composition of embodiment 17, wherein the oligomeric compound is present in the dosage unit at an amount selected from: less than about 300 mg, less than about 295 mg, less than about 290 mg, less than about 285 mg, less than about 280 mg, less than about 275 mg, less than about 270 mg, less than about 265 mg, less than about 260 mg, less than about 255 mg, less than about 250 mg, less than about 245 mg, less than about 240 mg, less than about 235 mg, less than about 230 mg, less than about 225 mg, less than about 220 mg, less than about 215 mg, less than about 210 mg, less than about 205 mg, less than about 200 mg, less than about 195 mg, less than about 190 mg, less than about 185 mg, less than about 180 mg, less than about 175 mg, less than about 170 mg, less than about 165 mg, less than about 160 mg, less than about 150 mg, less than about 145 mg, less than about 140 mg, less than about 135 mg, less than about 130 mg, less than about 125 mg, less than about 120 mg, less than about 115 mg, less than about 110 mg, less than about 105 mg, less than about 100 mg, less than about 95 mg, less than about 90 mg, less than about 85 mg, less than about 80 mg, less than about 75 mg, less than about 70 mg, less than about 65 mg, less than about 60 mg, less than about 55 mg, less than about 50 mg, less than about 45 mg, less than about 40 mg, less than about 35 mg, less than about 30 mg, less than about 25 mg, and less than about 20 mg.

Embodiment 22. The pharmaceutical composition of embodiment 19, wherein the oligomeric compound is present in the dosage unit at an amount selected from:

a) 10 mg to 140 mg, from 10 mg to 130 mg, from 10 mg to 120 mg, from 10 mg to 110 mg, from 10 mg to 100 mg, from 10 mg to 90 mg, from 10 mg to 80 mg, from 10 mg to 70 mg, from 10 mg to 60 mg, from 10 mg to 50 mg, from 10 mg to 40 mg, from 10 mg to 30 mg, from 10 mg to 20 mg, from 20 mg to 140 mg, from 20 mg to 130 mg, from 20 mg to 120 mg, from 20 mg to 110 mg, from 20 mg to 100 mg, from 20 mg to 90 mg, from 20 mg to 80 mg, from 20 mg to 70 mg, from 20 mg to 60 mg, from 20 mg to 50 mg, from 20 mg to 40 mg, from 20 mg to 30 mg, from 30 mg to 140 mg, from 30 mg to 130 mg, from 30 mg to 120 mg, from 30 mg to 110 mg, from 30 mg to 100 mg, from 30 mg to 90 mg, from 30 mg to 80mg, from 30 mg to 70 mg, from 30 mg to 60 mg, from 30 mg to 50 mg, from 30 mg to 40mg, from 40 mg to 140 mg, from 40 mg to 130 mg, from 40 mg to 120 mg, from from 40 mg to 110 mg, from 40 mg to 100 mg, from 40 mg to 90 mg, from 40 mg to 80 mg, from 40 mg to 70 mg, from 40 mg to 60 mg, from 40 mg to 50 mg, from 50 mg to 140 mg, from 50 mg to 130 mg, from 50 mg to 120 mg, from 50 mg to 110 mg, from 50 mg to 100 mg, from 50 mg to 90 mg, from 50 mg to 80 mg, from 50 mg to 70 mg, from 50 mg to 60 mg, from 60 mg to 140 mg, from 60 mg to 130 mg, from 60 mg to 120 mg, from 60 mg to 110 mg, from 60 mg to 100 mg, from 60 mg to 90 mg, from 60 mg to 80 mg, from 60 mg to 70 mg, from 70 mg to 140 mg, from 70 mg to 130 mg, from 70 mg to 120 mg, from 70 mg to 110 mg, from 70 mg to 100 mg, from 70 mg to 90 mg, from 70 mg to 80 mg, from 80 mg to 140 mg, from 80 mg to 130 mg, from 80 mg to 120 mg, from 80 mg to 110 mg, from 80 mg to 100 mg, from 80 mg to 90 mg, from 90 mg to 140 mg, from 90 mg to 130 mg, from 90 mg to 120 mg, from 90 mg to 110mg, from 90 mg to 100 mg, from 100 mg to 140 mg, from 100 mg to 130 mg, from 100 mg to 120 mg, from 100 mg to 110 mg, from 110 mg to 140 mg, from 110 mg to 130 mg, from 110 mg to 120 mg, from 120 mg to 140 mg,

from 120 mg to 130 mg, from 130 mg to 140 mg, from 65 mg to 95 mg, from 65 mg to 90 mg, from 65 mg to 85 mg from 65 mg to 80 mg, from 65 mg to 75 mg, from 65 mg to 70 mg, from 70 mg to 95 mg, from 70 mg to 85 mg, from 70 mg to 75 mg, from 75 mg to 100 mg, from 75 mg to 95 mg, from 75 mg to 90 mg, from 75 mg to 85 mg, from 75 mg to 80 mg, from 80 mg to 95 mg, from 80 mg to 85 mg, from 85 mg to 100 mg, from 85 mg to 90 mg, from 90 mg to 95 mg, from 95 mg to 100 mg, from 80 mg to 89 mg, from 80 mg to 88 mg, from 80 mg to 87 mg, from 80 mg to 86 mg, from 80 mg to 84 mg, from 80 mg to 83 mg, from 80 mg to 82 mg, from 80 mg to 81 mg, from 81 mg to 90 mg, from 82 mg to 89 mg, from 82 mg to 88 mg, from 82 mg to 87 mg, from 82 mg to 86 mg, from 82 mg to 85 mg, from 82 mg to 84 mg, from 82 mg to 83 mg, from 83 mg to 90 mg, from 83 mg to 89 mg, from 83 mg to 88 mg, from 83 mg to 87 mg, from 83 mg to 86 mg, from 83 mg to 85 mg, from 83 mg to 84 mg, from 84 mg to 90 mg, from 84 mg to 89 mg, from 84 mg to 88 mg, from 84 mg to 87 mg, from 84 mg to 86 mg, from 84 mg to 85 mg, from 85 mg to 89 mg, from 85 mg to 88 mg, from 85 mg to 87 mg, from 85 mg to 86 mg, from 86 mg to 90 mg, from 86 mg to 89 mg, from 86 mg to 88 mg, from 86 mg to 87 mg, from 87 mg to 90 mg, from 87 mg to 89 mg, from 87 mg to 88 mg, from 88 mg to 90 mg, from 88 mg to 89 mg, from 89 mg to 90 mg; and

b) less than about 300 mg, less than about 295 mg, less than about 290 mg, less than about 285 mg, less than about 280 mg, less than about 275 mg, less than 270 mg, less than 265 mg, less than about 260 mg, less than 255 mg, less than about 250 mg, less than about 245 mg, less than about 240 mg, less than about 235 mg, less than about 230 mg, less than about 225 mg, less than about 220 mg, less than about 215 mg, less than about 210 mg, less than about 205 mg, less than about 200 mg, less than about 195 mg, less than about 190 mg, less than about 185 mg, less than about 180 mg, less than about 175 mg, less than about 170 mg, less than about 165 mg, less than about 160 mg, less than about 150 mg, less than about 145 mg, less than about 140 mg, less than about 135 mg, less than about 130 mg, less than about 125 mg, less than about 120 mg, less than about 115 mg, less than about 110 mg, less than about 105 mg, less than about 100 mg, less than about 95 mg, less than about 90 mg, less than about 85 mg, less than about 80 mg, less than about 75 mg, less than about 70 mg, less than about 65 mg, less than about 60 mg, less than about 55 mg, less than about 50 mg, less than about 45 mg, less than about 40 mg, less than about 35 mg, less than about 30 mg, less than about 25 mg, and less than about 20 mg..

Embodiment 23. The pharmaceutical composition of embodiment 19, wherein the oligomeric compound is present in the dosage unit at an amount selected from:

a) at least about 10 mg, at least about 15 mg, at least about 20 mg, at least about 25 mg, at least about 30 mg, at least about 35 mg, at least about 40 mg, at least about 45 mg, at least about 50 mg, at least about 55 mg, at least about 60 mg, at least about 65 mg, at least about 70 mg, at least about 75 mg, at least about 80 mg, at least about 85 mg, at least about 90 mg, at least about 95 mg, at least about 100 mg, at least about 105 mg, at least about 115 mg, at least about 120 mg, at least about 125 mg, at least about 130 mg, at least about 135 mg, at least about 140 mg, at least about 145 mg, at least about 150 mg; and

b) at least 10 mg, at least 15 mg, at least 20 mg, at least 25 mg, at least 30 mg, at least 35 mg, at least 40 mg, at least 45 mg, at least 50 mg, at least 55 mg, at least 60 mg, at least 65 mg, at least 70 mg, at least 75 mg, at least 80 mg, at least 85 mg, at least 90 mg, at least 95 mg, at least about 100 mg, at least 105 mg, at least 115 mg, at least 120 mg, at least 125 mg, at least 130 mg, at least 135 mg, at least 140 mg, at least 145 mg, and at least 150 mg.

Embodiment 24. The pharmaceutical composition of any one of embodiments 19-23, wherein the dosage unit has a volume selected from:

a) 0.1 ml to 1.5 ml, 0.1 ml to 1.4 ml, 0.1 ml to 1.3 ml, 0.1 ml to 1.2 ml, 0.1 ml to 1.1 ml, 0.1 ml to 1.0 ml, 0.1 ml to 0.9 ml, 0.1 ml to 0.8 ml, 0.1 ml to 0.7 ml, 0.1 ml to 0.6 ml, 0.1 ml to 0.5 ml, 0.1 ml to 0.4 ml, 0.1 ml to 0.3 ml, 0.1 ml to 0.2 ml, 0.2 ml to 1.5 ml, 0.2 ml to 1.4 ml, 0.2 ml to 1.3 ml, 0.2 ml to 1.2 ml, 0.2 ml to 1.1 ml, 0.2 ml to 1.0 ml, 0.2 ml to 0.9 ml, 0.2 ml to 0.8 ml, 0.2 ml to 0.7 ml, 0.2 ml to 0.6 ml, 0.2 ml to 0.5 ml, 0.2 ml to 0.4 ml, 0.2 ml to 0.3 ml, 0.3 ml to 1.5ml, 0.3 ml to 1.4 ml, 0.3 ml to 1.3 ml, 0.3 ml to 1.2 ml, 0.3 ml to 1.1 ml, 0.3 ml to 1.0 ml, 0.3 ml to 0.9 ml, 0.3 ml to 0.8 ml, 0.3 ml to 0.7 ml, 0.3 ml to 0.6 ml, 0.3 ml to 0.5 ml, 0.3 ml to 0.4 ml, 0.4 ml to 1.5 ml, 0.4 ml to 1.4 ml, 0.4 ml to 1.3 ml, 0.4 ml to 1.2 ml, 0.4 ml to 1.1 ml, 0.4 ml to 1.0 ml, 0.4 ml to 0.9 ml, 0.4 ml to 0.8 ml, 0.4 ml to 0.7 ml, 0.4 ml to 0.6 ml, 0.4 ml to 0.5 ml, 0.5 ml to 1.5 ml, 0.5 ml to 1.4 ml, 0.5 ml to 1.3 ml, 0.5. ml to 1.2 ml, 0.5 ml to 1.1 ml, 0.5 ml to 1.0 ml, 0.5 ml to 0.9 ml, 0.5 ml to 0.8 ml, 0.5 ml to 0.7 ml, 0.5 ml to 0.6 ml, 0.6 ml to 1.5 ml, 0.6 ml to 1.4 ml, 0.6 mo to 1.3 ml, 0.6 ml to 1.2 ml, 0.6 ml to 1.1 ml, 0.6 ml to 1.0 ml, 0.6 ml to 0.9 ml, 0.6 ml to 0.8 ml, 0.6 ml to 0.7 ml, 0.7 ml, to 1.5 ml, 0.7 ml to 1.4 ml, 0.7 ml to 1.3 ml, 0.7 ml to 1.2 ml, 0.7 ml to 1.1 ml, 0.7 ml to 1.0 ml, 0.7 ml to 0.9 ml, 0.7 ml to 0.8 ml, 0.8 ml to 1.5 ml, 0.8 ml to 1.4 ml, 0.8 ml to 1.3 ml, 0.8 ml to 1.2 ml, 0.8 ml to 1.1 ml, 0.8 ml to 1.0 ml. 0.8 ml to 0.9 ml, 0.9 ml, to 1.5 ml, 0.9 ml to 1.4 ml, 0.9 ml to 1.3 ml, 0.9 ml to 1.2 ml, 0.9 ml, to 1.1 ml, 0.9 ml to 1.0 ml, 1.0 ml to 1.5 ml, 1.0 ml to 1.4 ml, 1.0 ml to 1.3 ml, 1.0 ml to 1.2 ml, 1.0 ml to 1.1 ml, 1.1 ml to 1.5 ml, 1.1 ml to 1.4 ml, 1.1 ml to 1.3 ml, 1.1 ml to 1.2 ml, 1.2 ml to 1.5 ml, 1.2 ml to 1.4 ml, 1.2 ml to 1.3 ml, 1.3 ml to 1.5 ml, 1.3 ml to 1.4 ml, 1.4 ml to, 1.5ml; and

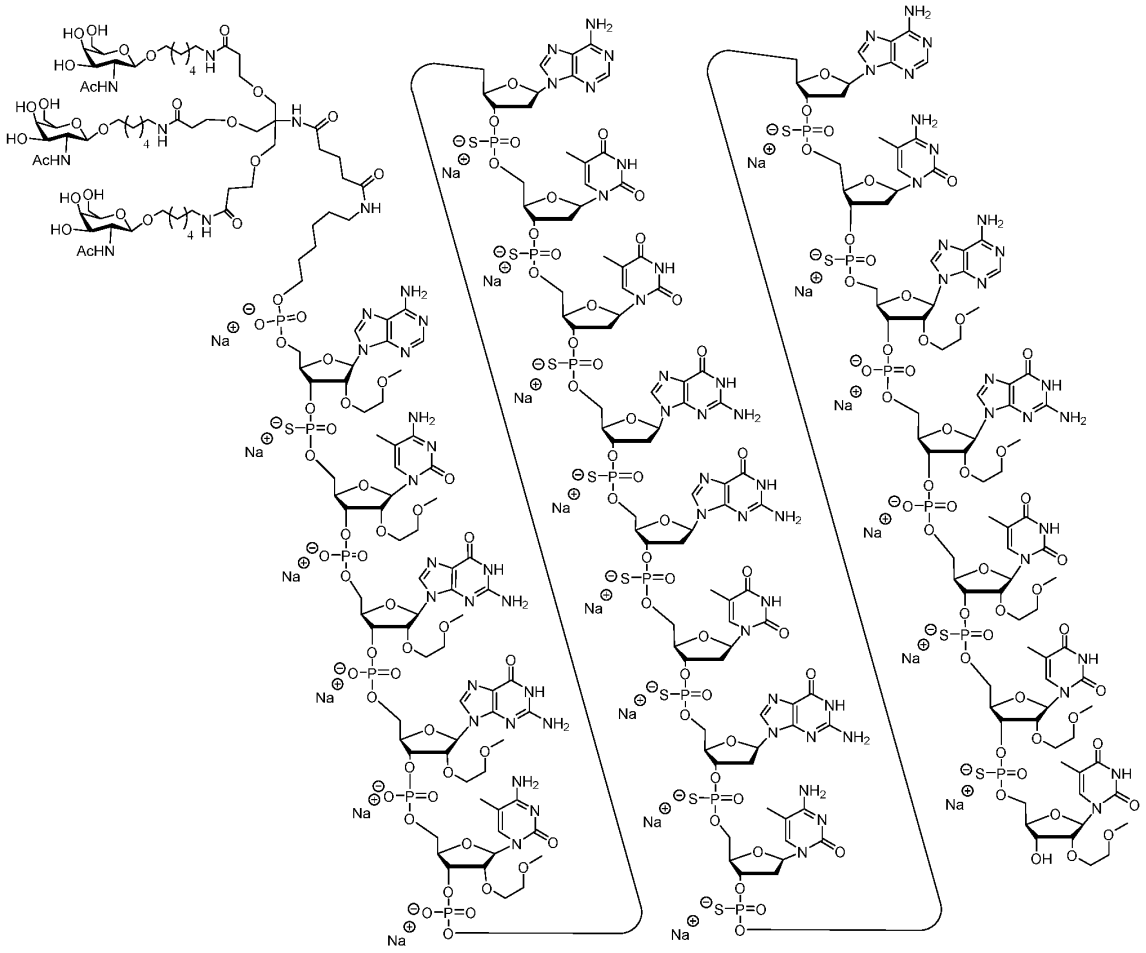
b) about 0.1 ml to about 1.5 ml, about 0.1 ml to about 1.4 ml, about 0.1 ml to about 1.3 ml, about 0.1 ml to about 1.2 ml, about 0.1 ml to about 1.1 ml, about 0.1 ml to about 1.0 ml, about 0.1 ml to about 0.9 ml, about 0.1 ml to about 0.8 ml, about 0.1 ml to about 0.7 ml, about 0.1 ml to about 0.6 ml, about 0.1 ml to about 0.5 ml, about 0.1 ml to about 0.4 ml, about 0.1 ml to about 0.3 ml, about 0.1 ml to about 0.2 ml, about 0.2 ml to about 1.5 ml, about 0.2 ml to about 1.4 ml, about 0.2 ml to about 1.3 ml, about 0.2 ml to about 1.2 ml, about 0.2 ml to about 1.1 ml, about 0.2 ml to about 1.0 ml, about 0.2 ml to about 0.9 ml, about 0.2 ml to about 0.8 ml, about 0.2 ml to about 0.7 ml, about 0.2 ml to about 0.6 ml, about 0.2 ml to about 0.5 ml, about 0.2 ml to about 0.4 ml, about 0.2 ml to about 0.3 ml, about 0.3 ml to about 1.5ml, about 0.3 ml to about 1.4 ml, about 0.3 ml to about 1.3 ml, about 0.3 ml to about 1.2 ml, about 0.3 ml to about 1.1 ml, about 0.3 ml to about 1.0 ml, about 0.3 ml to about 0.9 ml, about 0.3 ml to about 0.8 ml, about 0.3 ml to about 0.7 ml, about 0.3 ml to about 0.6 ml, about 0.3 ml to about 0.5 ml, about 0.3 ml to

about 0.4 ml, about 0.4 ml to about 1.5 ml, about 0.4 ml to about 1.4 ml, about 0.4 ml to about 1.3 ml, about 0.4 ml to about 1.2 ml, about 0.4 ml to about 1.1 ml, about 0.4 ml to about 1.0 ml, about 0.4 ml to about 0.9 ml, about 0.4 ml to about 0.8 ml, about 0.4 ml to about 0.7 ml, about 0.4 ml to about 0.6 ml, about 0.4 ml to about 0.5 ml, about 0.5 ml to about 1.5 ml, about 0.5 ml to about 1.4 ml, about 0.5 ml to about 1.3 ml, about 0.5. ml to about 1.2 ml, about 0.5 ml to about 1.1 ml, about 0.5 ml to about 1.0 ml, about 0.5 ml to about 0.9 ml, about 0.5 ml to about 0.8 ml, about 0.5 ml to about 0.7 ml, about 0.5 ml to about 0.6 ml, about 0.6 ml to about 1.5 ml, about 0.6 ml to about 1.4 ml, about 0.6 ml to about 1.3 ml, about 0.6 ml to about 1.2 ml, about 0.6 ml to about 1.1 ml, about 0.6 ml to about 1.0 ml, about 0.6 ml to about 0.9 ml, about 0.6 ml to about 0.8 ml, about 0.6 ml to about 0.7 ml, about 0.7 ml, about to about 1.5 ml, about 0.7 ml to about 1.4 ml, about 0.7 ml to about 1.3 ml, about 0.7 ml to about 1.2 ml, about 0.7 ml to about 1.1 ml, about 0.7 ml to about 1.0 ml, about 0.7 ml to about 0.9 ml, about 0.7 ml to about 0.8 ml, about 0.8 ml to about 1.5 ml, about 0.8 ml to about 1.4 ml, about 0.8 ml to about 1.3 ml, about 0.8 ml to about 1.2 ml, about 0.8 ml to about 1.1 ml, about 0.8 ml to about 1.0 ml. 0.8 ml to about 0.9 ml, about 0.9 ml, about to about 1.5 ml, about 0.9 ml to about 1.4 ml, about 0.9 ml to about 1.3 ml, about 0.9 ml to about 1.2 ml, about 0.9 ml, about to about 1.1 ml, about 0.9 ml to about 1.0 ml, about 1.0 ml to about 1.5 ml, about 1.0 ml to about 1.4 ml, about 1.0 ml to about 1.3 ml, about 1.0 ml to about 1.2 ml, about 1.0 ml to about 1.1 ml, about 1.1 ml to about 1.5 ml, about 1.1 ml to about 1.4 ml, about 1.1 ml to about 1.3 ml, about 1.1 ml to about 1.2 ml, about 1.2 ml to about 1.5 ml, about 1.2 ml to about 1.4 ml, about 1.2 ml to about 1.3 ml, about 1.3 ml to about 1.5 ml, about 1.3 ml to about 1.4 ml, and about 1.4 ml to about 1.5ml.

Embodiment 25. The pharmaceutical composition of any one of embodiments 14-24, wherein the pharmaceutical composition is packaged in a pre-filled syringe.

Embodiment 26. A method comprising contacting a cell with the oligomeric compound of any of embodiments 1-5.

Embodiment 27. A method comprising administering to an animal a pharmaceutical composition comprising a therapeutically effective amount of an oligomeric compound according to the following formula:



(SEQ ID NO: 3).

Embodiment 28. A method comprising administering to an animal a therapeutically effective amount of the oligomeric compound of any of embodiments 1-5 in the form of a pharmaceutical composition.

Embodiment 29. The method of embodiment 27 or 28, wherein the pharmaceutical composition consists or consists essentially of the oligomeric compound and phosphate buffered saline.

Embodiment 30. A method comprising administering to an animal the pharmaceutical compositions of any one of embodiments 14-25, wherein the pharmaceutical composition comprises a therapeutically effective amount of the oligomeric compound.

Embodiment 31. The method of embodiment 30, wherein the therapeutically effective amount does not significantly alter platelet levels or platelet activity in the animal or does not cause bleeding in the animal compared to an animal not administered the pharmaceutical composition.

Embodiment 32. The method of any one of embodiments 27 to 31, comprising administering an amount of the oligomeric compound selected from:

a) 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 105 mg, 110 mg, 115 mg, 120 mg, 125 mg, 130 mg, 135 mg, 140 mg, 145 mg, 150 mg, 155 mg, 160 mg, 165 mg, 170 mg, 175 mg, 180 mg, 185 mg, 190 mg, 195 mg, 200 mg, 205 mg, 210 mg, 215 mg, 220 mg, 225 mg, 230 mg, 235 mg, 240 mg, 245 mg, 250 mg, 255 mg, 260 mg, 265 mg, 270 mg, 275 mg, 280 mg, 285 mg, 290 mg, 295 mg, 300 mg;

b) about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg;

c) 20 mg, 21 mg, 22 mg, 23 mg, 24 mg, 25 mg, 26 mg, 27 mg, 28 mg, 29 mg, 30 mg, 31 mg, 32 mg, 33 mg, 34 mg, 35 mg, 36 mg, 37 mg, 38 mg, 39 mg, 40 mg, 41 mg, 42 mg, 43 mg, 44 mg, 45 mg, 46 mg, 47 mg, 48 mg, 49 mg, 50 mg, 51 mg, 52 mg, 53 mg, 54 mg, 55 mg, 56 mg, 57 mg, 58 mg, 59 mg, 60 mg, 61 mg, 62 mg, 63 mg, 64 mg, 65 mg, 66 mg, 67 mg, 68 mg, 69 mg, 70 mg, 71 mg, 72 mg, 73 mg, 74 mg, 75 mg, 76 mg, 77 mg, 78 mg, 79 mg, 80 mg, 81 mg, 82 mg, 83 mg, 84 mg, 85 mg, 86 mg, 87 mg, 88 mg, 89 mg, 90 mg, 91 mg, 92 mg, 93 mg, 94 mg, 95 mg, 96 mg, 97 mg, 98 mg, 99 mg, 100 mg, 101 mg, 102 mg, 103 mg, 104 mg, 105 mg, 106 mg, 107 mg, 108 mg, 109 mg, 110 mg, 111 mg, 112 mg, 113 mg, 114 mg, 115 mg, 116 mg, 117 mg, 118 mg, 119 mg, 120 mg, 121 mg, 122 mg, 123 mg, 124 mg, 125 mg, 126 mg, 127 mg, 128 mg, 129 mg, 130 mg, 131 mg, 132 mg, 133 mg, 134 mg, 135 mg, 136 mg, 137 mg, 138 mg, 139 mg, 140 mg;

d) about 20 mg, about 21 mg, about 22 mg, about 23 mg, about 24 mg, about 25 mg, about 26 mg, about 27 mg, about 28 mg, about 29 mg, about 30 mg, about 31 mg, about 32 mg, about 33 mg, about 34 mg, about 35 mg, about 36 mg, about 37 mg, about 38 mg, about 39 mg, about 40 mg, about 41 mg, about 42 mg, about 43 mg, about 44 mg, about 45 mg, about 46 mg, about 47 mg, about 48 mg, about 49 mg, about 50 mg, about 51 mg, about 52 mg, about 53 mg, about 54 mg, about 55 mg, about 56 mg, about 57 mg, about 58 mg, about 59 mg, about 60 mg, about 61 mg, about 62 mg, about 63 mg, about 64 mg, about 65 mg, about 66 mg, about 67 mg, about 68 mg, about 69 mg, about 70 mg, about 71 mg, about 72 mg, about 73 mg, about 74 mg, about 75 mg, about 76 mg, about 77 mg, about 78 mg, about 79 mg, about 80 mg, about 81 mg, about 82 mg, about 83 mg, about 84 mg, about 85 mg, about 86 mg, about 87 mg, about 88 mg, about 89 mg, about 90 mg, about 91 mg, about 92 mg, about 93 mg, about 94 mg, about 95 mg, about 96 mg, about 97 mg, about 98 mg, about 99 mg, about 100 mg, about 101 mg, about 102 mg, about 103 mg, about 104 mg, about 105 mg, about 106 mg, about 107 mg, about 108 mg,

about 109 mg, about 110 mg, about 111 mg, about 112 mg, about 113 mg, about 114 mg, about 115 mg, about 116 mg, about 117 mg, about 118 mg, about 119 mg, about 120 mg, about 121 mg, about 122 mg, about 123 mg, about 124 mg, about 125 mg, about 126 mg, about 127 mg, about 128 mg, about 129 mg, about 130 mg, about 131 mg, about 132 mg, about 133 mg, about 134 mg, about 135 mg, about 136 mg, about 137 mg, about 138 mg, about 139 mg, about 140 mg;

e) 75.0 mg, 75.1 mg, 75.2 mg, 75.3 mg, 75.4 mg, 75.5 mg, 75.6 mg, 75.7 mg, 75.8 mg, 75.9 mg, 76.0 mg, 76.1 mg, 76.2 mg, 76.3 mg. 76.4 mg, 76.5 mg, 76.6 mg, 76.7 mg, 76.8 mg, 76.9 mg, 77.0 mg, 77.1 mg, 77.2 mg, 77.3 mg, 77.4 mg, 77.5 mg, 77.6 mg, 77.7 mg, 77.8 mg, 77.9 mg, 78.0 mg, 78.1 mg, 78.2 mg, 78.3 mg. 78.4 mg, 78.5 mg, 78.6 mg, 78.7 mg, 78.8 mg, 78.9 mg, 79.0 mg, 79.1 mg, 79.2 mg, 79.3 mg, 79.4 mg, 79.5 mg, 79.6 mg, 79.7 mg, 79.8 mg, 79.9 mg, 80.0 mg, 80.1 mg, 80.2 mg, 80.3 mg. 80.4 mg, 80.5 mg, 80.6 mg, 80.7 mg, 80.8 mg, 80.9 mg, 81.0 mg, 81.1 mg, 81.2 mg, 81.3 mg, 81.4 mg, 81.5 mg, 81.6 mg, 81.7 mg, 81.8 mg, 81.9 mg, 82.0 mg, 82.1 mg, 82.2 mg, 82.3 mg. 82.4 mg, 82.5 mg, 82.6 mg, 82.7 mg, 82.8 mg, 82.9 mg, 83.0 mg, 83.1 mg, 83.2 mg, 83.3 mg, 83.4 mg, 83.5 mg, 83.6 mg, 83.7 mg, 83.8 mg, 83.9 mg, 84.0 mg, 84.1 mg, 84.2 mg, 84.3 mg. 84.4 mg, 84.5 mg, 84.6 mg, 84.7 mg, 84.8 mg, 84.9 mg, 85.0 mg; and

f) about 75.0 mg, about 75.1 mg, about 75.2 mg, about 75.3 mg, about 75.4 mg, about 75.5 mg, about 75.6 mg, about 75.7 mg, about 75.8 mg, about 75.9 mg, about 76.0 mg, about 76.1 mg, about 76.2 mg, about 76.3 mg. about about 76.4 mg, about 76.5 mg, about 76.6 mg, about 76.6 about 76.7 mg, about 76.8 mg, about 76.9 mg, about 77.0 mg, about 77.1 mg, about 77.2 mg, about 77.3 mg, about 77.4 mg, about 77.5 mg, about 77.6 mg, about 77.7 mg, about 77.8 mg, about 77.9 mg, about 78.0 mg, about 78.1 mg, about 78.2 mg, about 78.3 mg. about 78.4 mg, about 78.5 mg, about 78.6 mg, about 78.7 mg, about 78.8 mg, about 78.9 mg, about 79.0 mg, about 79.1 mg, about 79.2 mg, about 79.3 mg, about 79.4 mg, about 79.5 mg, about 79.6 mg, about 79.7 mg, about 79.8 mg, about 79.9 mg, about 80.0 mg, about 80.1 mg, about 80.2 mg, about 80.3 mg. about 80.4 mg, about 80.5 mg, about 80.6 mg, about 80.7 mg, about 80.8 mg, about 80.9 mg, about 81.0 mg, about 81.1 mg, about 81.2 mg, about 81.3 mg, about 81.4 mg, about 81.5 mg, about 81.6 mg, about 81.7 mg, about 81.8 mg, about 81.9 mg, about 82.0 mg, about 82.1 mg, about 82.2 mg, about 82.3 mg. about 82.4 mg, about 82.5 mg, about 82.6 mg, about 82.7 mg, about 82.8 mg, about 82.9 mg, about 83.0 mg, about 83.1 mg, about 83.2 mg, about 83.3 mg, about 83.4 mg, about 83.5 mg, about 83.6 mg, about 83.7 mg, about 83.8 mg, about 83.9 mg, about 84.0 mg, about 84.1 mg, about 84.2 mg, about 84.3 mg. about 84.4 mg, about 84.5 mg, about 84.6 mg, about 84.7 mg, about 84.8 mg, about 84.9 mg, and about 85.0 mg.

Embodiment 33. The method of any one of embodiments 27 to 31, comprising administering an amount of the oligomeric compound selected from: less than about 300 mg, less than about 295 mg, less than about 290 mg, less than about 285 mg, less than about 280 mg, less than about 275 mg, less than about 270 mg, less than about 265 mg, less than about 260 mg, less than about 255 mg, less than about 250 mg, less than about 245 mg, less than about 240 mg, less than about 235 mg, less than about 230 mg, less than about

225 mg, less than about 220 mg, less than about 215 mg, less than about 210 mg, less than about 205 mg, less than about 200 mg, less than about 195 mg, less than about 190 mg, less than about 185 mg, less than about 180 mg, less than about 175 mg, less than about 170 mg, less than about 165 mg, less than about 160 mg, less than about 150 mg, less than about 145 mg, less than about 140 mg, less than about 135 mg, less than about 130 mg, less than about 125 mg, less than about 120 mg, less than about 115 mg, less than about 110 mg, less than about 105 mg, less than about 100 mg, less than about 95 mg, less than about 90 mg, less than about 85 mg, less than about 80 mg, less than about 75 mg, less than about 70 mg, less than about 65 mg, less than about 60 mg, less than about 55 mg, less than about 50 mg, less than about 45 mg, less than about 40 mg, less than about 35 mg, less than about 30 mg, less than about 25 mg, and less than about 20 mg.

Embodiment 34. The method of any one of embodiments 27 to 31, comprising administering an amount of the oligomeric compound selected from:

a) 10 mg to 140 mg, from 10 mg to 130 mg, from 10 mg to 120 mg, from 10 mg to 110 mg, from 10 mg to 100 mg, from 10 mg to 90 mg, from 10 mg to 80 mg, from 10 mg to 70 mg, from 10 mg to 60 mg, from 10 mg to 50 mg, from 10 mg to 40 mg, from 10 mg to 30 mg, from 10 mg to 20 mg, from 20 mg to 140 mg, from 20 mg to 130 mg, from 20 mg to 120 mg, from 20 mg to 110 mg, from 20 mg to 100 mg, from 20 mg to 90 mg, from 20 mg to 80 mg, from 20 mg to 70 mg, from 20 mg to 60 mg, from 20 mg to 50 mg, from 20 mg to 40 mg, from 20 mg to 30 mg, from 30 mg to 140 mg, from 30 mg to 130 mg, from 30 mg to 120 mg, from 30 mg to 110 mg, from 30 mg to 100 mg, from 30 mg to 90 mg, from 30 mg to 80mg, from 30 mg to 70 mg, from 30 mg to 60 mg, from 30 mg to 50 mg, from 30 mg to 40mg, from 40 mg to 140 mg, from 40 mg to 130 mg, from 40 mg to 120 mg, from from 40 mg to 110 mg, from 40 mg to 100 mg, from 40 mg to 90 mg, from 40 mg to 80 mg, from 40 mg to 70 mg, from 40 mg to 60 mg, from 40 mg to 50 mg, from 50 mg to 140 mg, from 50 mg to 130 mg, from 50 mg to 120 mg, from 50 mg to 110 mg, from 50 mg to 100 mg, from 50 mg to 90 mg, from 50 mg to 80 mg, from 50 mg to 70 mg, from 50 mg to 60 mg, from 60 mg to 140 mg, from 60 mg to 130 mg, from 60 mg to 120 mg, from 60 mg to 110 mg, from 60 mg to 100 mg, from 60 mg to 90 mg, from 60 mg to 80 mg, from 60 mg to 70 mg, from 70 mg to 140 mg, from 70 mg to 130 mg, from 70 mg to 120 mg, from 70 mg to 110 mg, from 70 mg to 100 mg, from 70 mg to 90 mg, from 70 mg to 80 mg, from 80 mg to 140 mg, from 80 mg to 130 mg, from 80 mg to 120 mg, from 80 mg to 110 mg, from 80 mg to 100 mg, from 80 mg to 90 mg, from 90 mg to 140 mg, from 90 mg to 130 mg, from 90 mg to 120 mg, from 90 mg to 110mg, from 90 mg to 100 mg, from 100 mg to 140 mg, from 100 mg to 130 mg, from 100 mg to 120 mg, from 100 mg to 110 mg, from 110 mg to 140 mg, from 110 mg to 130 mg, from 110 mg to 120 mg, from 120 mg to 140 mg, from 120 mg to 130 mg, from 130 mg to 140 mg, from 65 mg to 95 mg, from 65 mg to 90 mg, from 65 mg to 85 mg from 65 mg to 80 mg, from 65 mg to 75 mg, from 65 mg to 70 mg, from 70 mg to 95 mg, from 70 mg to 85 mg, from 70 mg to 75 mg, from 75 mg to 100 mg, from 75 mg to 95 mg, from 75 mg to 90 mg, from 75 mg to 85 mg, from 75 mg to 80 mg, from 80 mg to 95 mg, from 80 mg to 85 mg, from 85 mg to 100 mg, from 85 mg to 90 mg, from 90 mg to 95 mg, from 95 mg to 100 mg, from 80 mg to 89

mg, from 80 mg to 88 mg, from 80 mg to 87 mg, from 80 mg to 86 mg, from 80 mg to 84 mg, from 80 mg to 83 mg, from 80 mg to 82 mg, from 80 mg to 81 mg, from 81 mg to 90 mg, from 82 mg to 89 mg, from 82 mg to 88 mg, from 82 mg to 87 mg, from 82 mg to 86 mg, from 82 mg to 85 mg, from 82 mg to 84 mg, from 82 mg to 83 mg, from 83 mg to 90 mg, from 83 mg to 89 mg, from 83 mg to 88 mg, from 83 mg to 87 mg, from 83 mg to 86 mg, from 83 mg to 85 mg, from 83 mg to 84 mg, from 84 mg to 90 mg, from 84 mg to 89 mg, from 84 mg to 88 mg, from 84 mg to 87 mg, from 84 mg to 86 mg, from 84 mg to 85 mg, from 85 mg to 89 mg, from 85 mg to 88 mg, from 85 mg to 87 mg, from 85 mg to 86 mg, from 86 mg to 90 mg, from 86 mg to 89 mg, from 86 mg to 88 mg, from 86 mg to 87 mg, from 87 mg to 90 mg, from 87 mg to 89 mg, from 87 mg to 88 mg, from 88 mg to 90 mg, from 88 mg to 89 mg, from 89 mg to 90 mg; and

b) less than about 300 mg, less than about 295 mg, less than about 290 mg, less than about 285 mg, less than about 280 mg, less than about 275 mg, less than 270 mg, less than 265 mg, less than about 260 mg, less than 255 mg, less than about 250 mg, less than about 245 mg, less than about 240 mg, less than about 235 mg, less than about 230 mg, less than about 225 mg, less than about 220 mg, less than about 215 mg, less than about 210 mg, less than about 205 mg, less than about 200 mg, less than about 195 mg, less than about 190 mg, less than about 185 mg, less than about 180 mg, less than about 175 mg, less than about 170 mg, less than about 165 mg, less than about 160 mg, less than about 150 mg, less than about 145 mg, less than about 140 mg, less than about 135 mg, less than about 130 mg, less than about 125 mg, less than about 120 mg, less than about 115 mg, less than about 110 mg, less than about 105 mg, less than about 100 mg, less than about 95 mg, less than about 90 mg, less than about 85 mg, less than about 80 mg, less than about 75 mg, less than about 70 mg, less than about 65 mg, less than about 60 mg, less than about 55 mg, less than about 50 mg, less than about 45 mg, less than about 40 mg, less than about 35 mg, less than about 30 mg, less than about 25 mg, and less than about 20 mg..

Embodiment 35. The method of any one of embodiments 27 to 31, comprising administering an amount of the oligomeric compound selected from:

a) at least about 10 mg, at least about 15 mg, at least about 20 mg, at least about 25 mg, at least about 30 mg, at least about 35 mg, at least about 40 mg, at least about 45 mg, at least about 50 mg, at least about 55 mg, at least about 60 mg, at least about 65 mg, at least about 70 mg, at least about 75 mg, at least about 80 mg, at least about 85 mg, at least about 90 mg, at least about 95 mg, at least about 100 mg, at least about 105 mg, at least about 115 mg, at least about 120 mg, at least about 125 mg, at least about 130 mg, at least about 135 mg, at least about 140 mg, at least about 145 mg, at least about 150 mg; and

b) at least 10 mg, at least 15 mg, at least 20 mg, at least 25 mg, at least 30 mg, at least 35 mg, at least 40 mg, at least 45 mg, at least 50 mg, at least 55 mg, at least 60 mg, at least 65 mg, at least 70 mg, at least 75 mg, at least 80 mg, at least 85 mg, at least 90 mg, at least 95 mg, at least about 100 mg, at least 105 mg, at least 115 mg, at least 120 mg, at least 125 mg, at least 130 mg, at least 135 mg, at least 140 mg, at least 145 mg, and at least 150 mg.

Embodiment 36. The method of any one of embodiments 27 to 35, wherein the concentration of the oligomeric compound in the pharmaceutically acceptable carrier or diluent is selected from:

a) 5 mg/ml, 10 mg/ml, 15 mg/ml, 20 mg/ml, 25 mg/ml, 30 mg/ml, 35 mg/ml, 40 mg/ml, 45 mg/ml, 50 mg/ml, 55 mg/ml, 60 mg/ml, 65 mg/ml, 70 mg/ml, 75 mg/ml, 80 mg/ml, 85 mg/ml, 90 mg/ml, 95 mg/ml, 100 mg/ml, 105 mg/ml, 110 mg/ml, 115 mg/ml, 120 mg/ml, 125 mg/ml, 130 mg/ml, 135 mg/ml, 140 mg/ml, 145 mg/ml, 150 mg/ml, 155 mg/ml, 160 mg/ml;

b) about 5 mg/ml, about 10 mg/ml, about 15 mg/ml, about 20 mg/ml, about 25 mg/ml, about 30 mg/ml, about 35 mg/ml, about 40 mg/ml, about 45 mg/ml, about 50 mg/ml, about 55 mg/ml, about 60 mg/ml, about 65 mg/ml, about 70 mg/ml, about 75 mg/ml, about 80 mg/ml, about 85 mg/ml, about 90 mg/ml, about 95 mg/ml, about 100 mg/ml, about 105 mg/ml, about 110 mg/ml, about 115 mg/ml, about 120 mg/ml, about 125 mg/ml, about 130 mg/ml, about 135 mg/ml, about 140 mg/ml, about 145 mg/ml, about 150 mg/ml, about 155 mg/ml, about 160 mg/ml; and

c) 20 mg/ml, 21 mg/ml, 22 mg/ml, 23 mg/ml, 24 mg/ml, 25 mg/ml, 26 mg/ml, 27 mg/ml, 28 mg/ml, 29 mg/ml, 30 mg/ml, 31 mg/ml, 32 mg/ml, 33 mg/ml, 34 mg/ml, 35 mg/ml, 36 mg/ml, 37 mg/ml, 38 mg/ml, 39 mg/ml, 40 mg/ml, 41 mg/ml, 42 mg/ml, 43 mg/ml, 44 mg/ml, 45 mg/ml, 46 mg/ml, 47 mg/ml, 48 mg/ml, 49 mg/ml, 50 mg/ml, 51 mg/ml, 52 mg/ml, 53 mg/ml, 54 mg/ml, 55 mg/ml, 56 mg/ml, 57 mg/ml, 58 mg/ml, 59 mg/ml, 60 mg/ml, 61 mg/ml, 62 mg/ml, 63 mg/ml, 64 mg/ml, 65 mg/ml, 66 mg/ml, 67 mg/ml, 68 mg/ml, 69 mg/ml, 70 mg/ml, 71 mg/ml, 72 mg/ml, 73 mg/ml, 74 mg/ml, 75 mg/ml, 76 mg/ml, 77 mg/ml, 78 mg/ml, 79 mg/ml, 80 mg/ml, 81 mg/ml, 82 mg/ml, 83 mg/ml, 84 mg/ml, 85 mg/ml, 86 mg/ml, 87 mg/ml, 88 mg/ml, 89 mg/ml, 90 mg/ml, 91 mg/ml, 92 mg/ml, 93 mg/ml, 94 mg/ml, 95 mg/ml, 96 mg/ml, 97 mg/ml, 98 mg/ml, 99 mg/ml, 100 mg/ml, 101 mg/ml, 102 mg/ml, 103 mg/ml, 104 mg/ml, 105 mg/ml, 106 mg/ml, 107 mg/ml, 108 mg/ml, 109 mg/ml, 110 mg/ml, 111 mg/ml, 112 mg/ml, 113 mg/ml, 114 mg/ml, 115 mg/ml, 116 mg/ml, 117 mg/ml, 118 mg/ml, 119 mg/ml, 120 mg/ml, 121 mg/ml, 122 mg/ml, 123 mg/ml, 124 mg/ml, 125 mg/ml, 126 mg/ml, 127 mg/ml, 128 mg/ml, 129 mg/ml, 130 mg/ml, 131 mg/ml, 132 mg/ml, 133 mg/ml, 134 mg/ml, 135 mg/ml, 136 mg/ml, 137 mg/ml, 138 mg/ml, 139 mg/ml, 140 mg/ml;

d) about 20 mg/ml, about 21 mg/ml, about 22 mg/ml, about 23 mg/ml, about 24 mg/ml, about 25 mg/ml, about 26 mg/ml, about 27 mg/ml, about 28 mg/ml, about 29 mg/ml, about 30 mg/ml, about 31 mg/ml, about 32 mg/ml, about 33 mg/ml, about 34 mg/ml, about 35 mg/ml, about 36 mg/ml, about 37 mg/ml, about 38 mg/ml, about 39 mg/ml, about 40 mg/ml, about 41 mg/ml, about 42 mg/ml, about 43 mg/ml, about 44 mg/ml, about 45 mg/ml, about 46 mg/ml, about 47 mg/ml, about 48 mg/ml, about 49 mg/ml, about 50 mg/ml, about 51 mg/ml, about 52 mg/ml, about 53 mg/ml, about 54 mg/ml, about 55 mg/ml, about 56 mg/ml, about 57 mg/ml, about 58 mg/ml, about 59 mg/ml, about 60 mg/ml, about 61 mg/ml, about 62 mg/ml, about 63 mg/ml, about 64 mg/ml, about 65 mg/ml, about 66 mg/ml, about 67 mg/ml, about 68 mg/ml, about 69 mg/ml, about 70 mg/ml, about 71 mg/ml, about 72 mg/ml, about 73 mg/ml, about 74 mg/ml, about 75 mg/ml, about 76 mg/ml, about 77 mg/ml, about 78 mg/ml, about 79

mg/ml, about 80 mg/ml, about 81 mg/ml, about 82 mg/ml, about 83 mg/ml, about 84 mg/ml, about 85 mg/ml, about 86 mg/ml, about 87 mg/ml, about 88 mg/ml, about 89 mg/ml, about 90 mg/ml, about 91 mg/ml, about 92 mg/ml, about 93 mg/ml, about 94 mg/ml, about 95 mg/ml, about 96 mg/ml, about 97 mg/ml, about 98 mg/ml, about 99 mg/ml, about 100 mg/ml, about 101 mg/ml, about 102 mg/ml, about 103 mg/ml, about 104 mg/ml, about 105 mg/ml, about 106 mg/ml, about 107 mg/ml, about 108 mg/ml, about 109 mg/ml, about 110 mg/ml, about 111 mg/ml, about 112 mg/ml, about 113 mg/ml, about 114 mg/ml, about 115 mg/ml, about 116 mg/ml, about 117 mg/ml, about 118 mg/ml, about 119 mg/ml, about 120 mg/ml, about 121 mg/ml, about 122 mg/ml, about 123 mg/ml, about 124 mg/ml, about 125 mg/ml, about 126 mg/ml, about 127 mg/ml, about 128 mg/ml, about 129 mg/ml, about 130 mg/ml, about 131 mg/ml, about 132 mg/ml, about 133 mg/ml, about 134 mg/ml, about 135 mg/ml, about 136 mg/ml, about 137 mg/ml, about 138 mg/ml, about 139 mg/ml, and about 140 mg/ml.

Embodiment 37. The method of any one of embodiments 27 to 35, wherein the concentration of the oligomeric compound in the pharmaceutically acceptable carrier or diluent is selected from: 20 mg/ml to 180 mg/ml, 20 mg/ml to 170 mg, 20 mg/ml to 160 mg/ml, 20 mg/ml to 150 mg/ml, 20 mg/ml to 140 mg/ml, 20 mg/ml to 130 mg/ml, 20 mg/ml to 120 mg/ml, 20 mg/ml to 110 mg/ml, 20 mg/ml to 100 mg/ml, 20 mg/ml to 90 mg/ml, 20 mg/ml to 80 mg/ml, 20 mg/ml to 70 mg/ml, 20 mg/ml to 60 mg/ml, 20 mg/ml to 50 mg/ml, 20 mg/ml to 40 mg/ml, 20 mg/ml to 30 mg/ml, 30 mg/ml to 180 mg/ml, 30 mg/ml to 170 mg, 30 mg/ml to 160 mg/ml, 30 mg/ml to 150 mg/ml, 30 mg/ml to 140 mg/ml, 30 mg/ml to 130 mg/ml, 30 mg/ml to 120 mg/ml, 30 mg/ml to 110 mg/ml, 30 mg/ml to 100 mg/ml, 30 mg/ml to 90 mg/ml, 30 mg/ml to 80 mg/ml, 30 mg/ml to 70 mg/ml, 30 mg/ml to 60 mg/ml, 30 mg/ml to 50 mg/ml, 30 mg/ml to 40 mg/ml, 40 mg/ml to 180 mg/ml, 40 mg/ml to 170 mg, 40 mg/ml to 160 mg/ml, 40 mg/ml to 150 mg/ml, 40 mg/ml to 140 mg/ml, 40 mg/ml to 130 mg/ml, 40 mg/ml to 120 mg/ml, 40 mg/ml to 110 mg/ml, 40 mg/ml to 100 mg/ml, 40 mg/ml to 90 mg/ml, 40 mg/ml to 80 mg/ml, 40 mg/ml to 70 mg/ml, 40 mg/ml to 60 mg/ml, 40 mg/ml to 50 mg/ml, 50 mg/ml to 180 mg/ml, 50 mg/ml to 170 mg, 50 mg/ml to 160 mg/ml, 50 mg/ml to 150 mg/ml, 50 mg/ml to 140 mg/ml, 50 mg/ml to 130 mg/ml, 50 mg/ml to 120 mg/ml, 50 mg/ml to 110 mg/ml, 50 mg/ml to 100 mg/ml, 50 mg/ml to 90 mg/ml, 50 mg/ml to 80 mg/ml, 50 mg/ml to 70 mg/ml, 50 mg/ml to 60 mg/ml, 60 mg/ml to 180 mg/ml, 60 mg/ml to 170 mg, 60 mg/ml to 160 mg/ml, 60 mg/ml to 150 mg/ml, 60 mg/ml to 140 mg/ml, 60 mg/ml to 130 mg/ml, 60 mg/ml to 120 mg/ml, 60 mg/ml to 110 mg/ml, 60 mg/ml to 100 mg/ml, 60 mg/ml to 90 mg/ml, 60 mg/ml to 80 mg/ml, 60 mg/ml to 70 mg/ml, 70 mg/ml to 180 mg/ml, 70 mg/ml to 170 mg, 70 mg/ml to 160 mg/ml, 70 mg/ml to 150 mg/ml, 70 mg/ml to 140 mg/ml, 70 mg/ml to 130 mg/ml, 70 mg/ml to 120 mg/ml, 70 mg/ml to 110 mg/ml, 70 mg/ml to 100 mg/ml, 70 mg/ml to 90 mg/ml, 70 mg/ml to 80 mg/ml, 80 mg/ml to 180 mg/ml, 80 mg/ml to 170 mg, 80 mg/ml to 160 mg/ml, 80 mg/ml to 150 mg/ml, 80 mg/ml to 140 mg/ml, 80 mg/ml to 130 mg/ml, 80 mg/ml to 120 mg/ml, 80 mg/ml to 110 mg/ml, 80 mg/ml to 100 mg/ml, 80 mg/ml to 90 mg/ml, 90 mg/ml to 180 mg/ml, 90 mg/ml to 170 mg, 90 mg/ml to 160 mg/ml, 90 mg/ml to 150 mg/ml, 90 mg/ml to 140 mg/ml, 90 mg/ml to 130 mg/ml, 90 mg/ml to 120 mg/ml, 90 mg/ml to 110 mg/ml, 90 mg/ml to 100 mg/ml, 100 mg/ml to 180 mg/ml, 100 mg/ml to 170

mg, 100 mg/ml to 160 mg/ml, 100 mg/ml to 150 mg/ml, 100 mg/ml to 140 mg/ml, 100 mg/ml to 130 mg/ml, 100 mg/ml to 120 mg/ml, 100 mg/ml to 110 mg/ml, 110 mg/ml to 180 mg/ml, 110 mg/ml to 170 mg, 110 mg/ml to 160 mg/ml, 110 mg/ml to 150 mg/ml, 110 mg/ml to 140 mg/ml, 110 mg/ml to 130 mg/ml, 110 mg/ml to 120 mg/ml, 120 mg/ml to 180 mg/ml, 120 mg/ml to 170 mg, 120 mg/ml to 160 mg/ml, 120 mg/ml to 150 mg/ml, 120 mg/ml to 140 mg/ml, 120 mg/ml to 130 mg/ml, 130 mg/ml to 180 mg/ml, 130 mg/ml to 170 mg, 130 mg/ml to 160 mg/ml, 130 mg/ml to 150 mg/ml, 130 mg/ml to 140 mg/ml, 140 mg/ml to 180 mg/ml, 140 mg/ml to 170 mg/ml, 140 mg/ml to 160 mg/ml, 140 mg/ml to 150 mg/ml, 150 mg/ml to 180 mg/ml, 150 mg/ml to 170 mg/ml, 150 mg/ml to 160 mg/ml, 160 mg/ml to 180 mg/ml, 160 mg/ml to 170 mg/ml, and 170 mg/ml to 180 mg/ml.

Embodiment 38. The method of any one of embodiments 27 to 37, wherein the pharmaceutical composition is a form of a dosage unit, wherein the dosage unit is characterized by a volume selected from:

a) 0.1 ml to 1.5 ml, 0.1 ml to 1.4 ml, 0.1 ml to 1.3 ml, 0.1 ml to 1.2 ml, 0.1 ml to 1.1 ml, 0.1 ml to 1.0 ml, 0.1 ml to 0.9 ml, 0.1 ml to 0.8 ml, 0.1 ml to 0.7 ml, 0.1 ml to 0.6 ml, 0.1 ml to 0.5 ml, 0.1 ml to 0.4 ml, 0.1 ml to 0.3 ml, 0.1 ml to 0.2 ml, 0.2 ml to 1.5 ml, 0.2 ml to 1.4 ml, 0.2 ml to 1.3 ml, 0.2 ml to 1.2 ml, 0.2 ml to 1.1 ml, 0.2 ml to 1.0 ml, 0.2 ml to 0.9 ml, 0.2 ml to 0.8 ml, 0.2 ml to 0.7 ml, 0.2 ml to 0.6 ml, 0.2 ml to 0.5 ml, 0.2 ml to 0.4 ml, 0.2 ml to 0.3 ml, 0.3 ml to 1.5ml, 0.3 ml to 1.4 ml, 0.3 ml to 1.3 ml, 0.3 ml to 1.2 ml, 0.3 ml to 1.1 ml, 0.3 ml to 1.0 ml, 0.3 ml to 0.9 ml, 0.3 ml to 0.8 ml, 0.3 ml to 0.7 ml, 0.3 ml to 0.6 ml, 0.3 ml to 0.5 ml, 0.3 ml to 0.4 ml, 0.4 ml to 1.5 ml, 0.4 ml to 1.4 ml, 0.4 ml to 1.3 ml, 0.4 ml to 1.2 ml, 0.4 ml to 1.1 ml, 0.4 ml to 1.0 ml, 0.4 ml to 0.9 ml, 0.4 ml to 0.8 ml, 0.4 ml to 0.7 ml, 0.4 ml to 0.6 ml, 0.4 ml to 0.5 ml, 0.5 ml to 1.5 ml, 0.5 ml to 1.4 ml, 0.5 ml to 1.3 ml, 0.5. ml to 1.2 ml, 0.5 ml to 1.1 ml, 0.5 ml to 1.0 ml, 0.5 ml to 0.9 ml, 0.5 ml to 0.8 ml, 0.5 ml to 0.7 ml, 0.5 ml to 0.6 ml, 0.6 ml to 1.5 ml, 0.6 ml to 1.4 ml, 0.6 mo to 1.3 ml, 0.6 ml to 1.2 ml, 0.6 ml to 1.1 ml, 0.6 ml to 1.0 ml, 0.6 ml to 0.9 ml, 0.6 ml to 0.8 ml, 0.6 ml to 0.7 ml, 0.7 ml, to 1.5 ml, 0.7 ml to 1.4 ml, 0.7 ml to 1.3 ml, 0.7 ml to 1.2 ml, 0.7 ml to 1.1 ml, 0.7 ml to 1.0 ml, 0.7 ml to 0.9 ml, 0.7 ml to 0.8 ml, 0.8 ml to 1.5 ml, 0.8 ml to 1.4 ml, 0.8 ml to 1.3 ml, 0.8 ml to 1.2 ml, 0.8 ml to 1.1 ml, 0.8 ml to 1.0 ml. 0.8 ml to 0.9 ml, 0.9 ml, to 1.5 ml, 0.9 ml to 1.4 ml, 0.9 ml to 1.3 ml, 0.9 ml to 1.2 ml, 0.9 ml, to 1.1 ml, 0.9 ml to 1.0 ml, 1.0 ml to 1.5 ml, 1.0 ml to 1.4 ml, 1.0 ml to 1.3 ml, 1.0 ml to 1.2 ml, 1.0 ml to 1.1 ml, 1.1 ml to 1.5 ml, 1.1 ml to 1.4 ml, 1.1 ml to 1.3 ml, 1.1 ml to 1.2 ml, 1.2 ml to 1.5 ml, 1.2 ml to 1.4 ml, 1.2 ml to 1.3 ml, 1.3 ml to 1.5 ml, 1.3 ml to 1.4 ml, 1.4 ml to, 1.5ml; and

b) about 0.1 ml to about 1.5 ml, about 0.1 ml to about 1.4 ml, about 0.1 ml to about 1.3 ml, about 0.1 ml to about 1.2 ml, about 0.1 ml to about 1.1 ml, about 0.1 ml to about 1.0 ml, about 0.1 ml to about 0.9 ml, about 0.1 ml to about 0.8 ml, about 0.1 ml to about 0.7 ml, about 0.1 ml to about 0.6 ml, about 0.1 ml to about 0.5 ml, about 0.1 ml to about 0.4 ml, about 0.1 ml to about 0.3 ml, about 0.1 ml to about 0.2 ml, about 0.2 ml to about 1.5 ml, about 0.2 ml to about 1.4 ml, about 0.2 ml to about 1.3 ml, about 0.2 ml to about 1.2 ml, about 0.2 ml to about 1.1 ml, about 0.2 ml to about 1.0 ml, about 0.2 ml to about 0.9 ml, about 0.2 ml to about 0.8 ml, about 0.2 ml to about 0.7 ml, about 0.2 ml to about 0.6 ml, about 0.2 ml to

about 0.5 ml, about 0.2 ml to about 0.4 ml, about 0.2 ml to about 0.3 ml, about 0.3 ml to about 1.5ml, about 0.3 ml to about 1.4 ml, about 0.3 ml to about 1.3 ml, about 0.3 ml to about 1.2 ml, about 0.3 ml to about 1.1 ml, about 0.3 ml to about 1.0 ml, about 0.3 ml to about 0.9 ml, about 0.3 ml to about 0.8 ml, about 0.3 ml to about 0.7 ml, about 0.3 ml to about 0.6 ml, about 0.3 ml to about 0.5 ml, about 0.3 ml to about 0.4 ml, about 0.4 ml to about 1.5 ml, about 0.4 ml to about 1.4 ml, about 0.4 ml to about 1.3 ml, about 0.4 ml to about 1.2 ml, about 0.4 ml to about 1.1 ml, about 0.4 ml to about 1.0 ml, about 0.4 ml to about 0.9 ml, about 0.4 ml to about 0.8 ml, about 0.4 ml to about 0.7 ml, about 0.4 ml to about 0.6 ml, about 0.4 ml to about 0.5 ml, about 0.5 ml to about 1.5 ml, about 0.5 ml to about 1.4 ml, about 0.5 ml to about 1.3 ml, about 0.5. ml to about 1.2 ml, about 0.5 ml to about 1.1 ml, about 0.5 ml to about 1.0 ml, about 0.5 ml to about 0.9 ml, about 0.5 ml to about 0.8 ml, about 0.5 ml to about 0.7 ml, about 0.5 ml to about 0.6 ml, about 0.6 ml to about 1.5 ml, about 0.6 ml to about 1.4 ml, about 0.6 ml to about 1.3 ml, about 0.6 ml to about 1.2 ml, about 0.6 ml to about 1.1 ml, about 0.6 ml to about 1.0 ml, about 0.6 ml to about 0.9 ml, about 0.6 ml to about 0.8 ml, about 0.6 ml to about 0.7 ml, about 0.7 ml, about to about 1.5 ml, about 0.7 ml to about 1.4 ml, about 0.7 ml to about 1.3 ml, about 0.7 ml to about 1.2 ml, about 0.7 ml to about 1.1 ml, about 0.7 ml to about 1.0 ml, about 0.7 ml to about 0.9 ml, about 0.7 ml to about 0.8 ml, about 0.8 ml to about 1.5 ml, about 0.8 ml to about 1.4 ml, about 0.8 ml to about 1.3 ml, about 0.8 ml to about 1.2 ml, about 0.8 ml to about 1.1 ml, about 0.8 ml to about 1.0 ml. 0.8 ml to about 0.9 ml, about 0.9 ml, about to about 1.5 ml, about 0.9 ml to about 1.4 ml, about 0.9 ml to about 1.3 ml, about 0.9 ml to about 1.2 ml, about 0.9 ml, about to about 1.1 ml, about 0.9 ml to about 1.0 ml, about 1.0 ml to about 1.5 ml, about 1.0 ml to about 1.4 ml, about 1.0 ml to about 1.3 ml, about 1.0 ml to about 1.2 ml, about 1.0 ml to about 1.1 ml, about 1.1 ml to about 1.5 ml, about 1.1 ml to about 1.4 ml, about 1.1 ml to about 1.3 ml, about 1.1 ml to about 1.2 ml, about 1.2 ml to about 1.5 ml, about 1.2 ml to about 1.4 ml, about 1.2 ml to about 1.3 ml, about 1.3 ml to about 1.5 ml, about 1.3 ml to about 1.4 ml, and about 1.4 ml to about 1.5ml.

Embodiment 39. The method of any one of embodiments 27-38, comprising administering a first dose and a second dose of the pharmaceutical composition.

Embodiment 40. The method of embodiment 39, wherein the first dose and the second dose are separated by 5, 10, 15, 20, 25, 30, 35, or 40 days.

Embodiment 41. The method of embodiment 39, wherein the first dose and the second dose are separated by 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 days.

Embodiment 42. The method of embodiment 39, wherein the first dose and the second dose are separated by 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 weeks.

Embodiment 43. The method of embodiment 39, wherein the first dose and the second dose are separated by 1, 2, 3, 4, 5, or 6 months.

Embodiment 44. The method of embodiment 39, comprising administering the pharmaceutical composition monthly or about monthly.

Embodiment 45. The method of embodiment 44, comprising administering the pharmaceutical composition for at least two months, at least three months, at least four months, at least five months, or at least six months.

Embodiment 46. The method of embodiment 39, comprising administering the pharmaceutical composition weekly or about weekly.

Embodiment 47. The method of embodiment 46, comprising administering the pharmaceutical composition to the animal weekly or about weekly for less than 2 weeks, less than 3 weeks, less than 4 weeks, less than 5 weeks, less than 6 weeks, less than 8 week, less than 12 weeks, less than 16 weeks, or less than 20 weeks.

Embodiment 48. The method of any one of embodiments 27-47, wherein administering comprises performing a subcutaneous injection on the animal.

Embodiment 49. The method of any one of embodiments 27-48, wherein administering comprises self-administration.

Embodiment 50. The method of any one of embodiments 27-47, wherein administering comprises performing an intravenous injection on the animal.

Embodiment 51. The method of any one of embodiments 27-50, comprising administering the pharmaceutical composition at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 8, or at least 10 times.

Embodiment 52. The method of any one of embodiments 27-50, comprising administering the pharmaceutical composition less than 20 times, less than 15 times, less than 10 times, or less than 5 times.

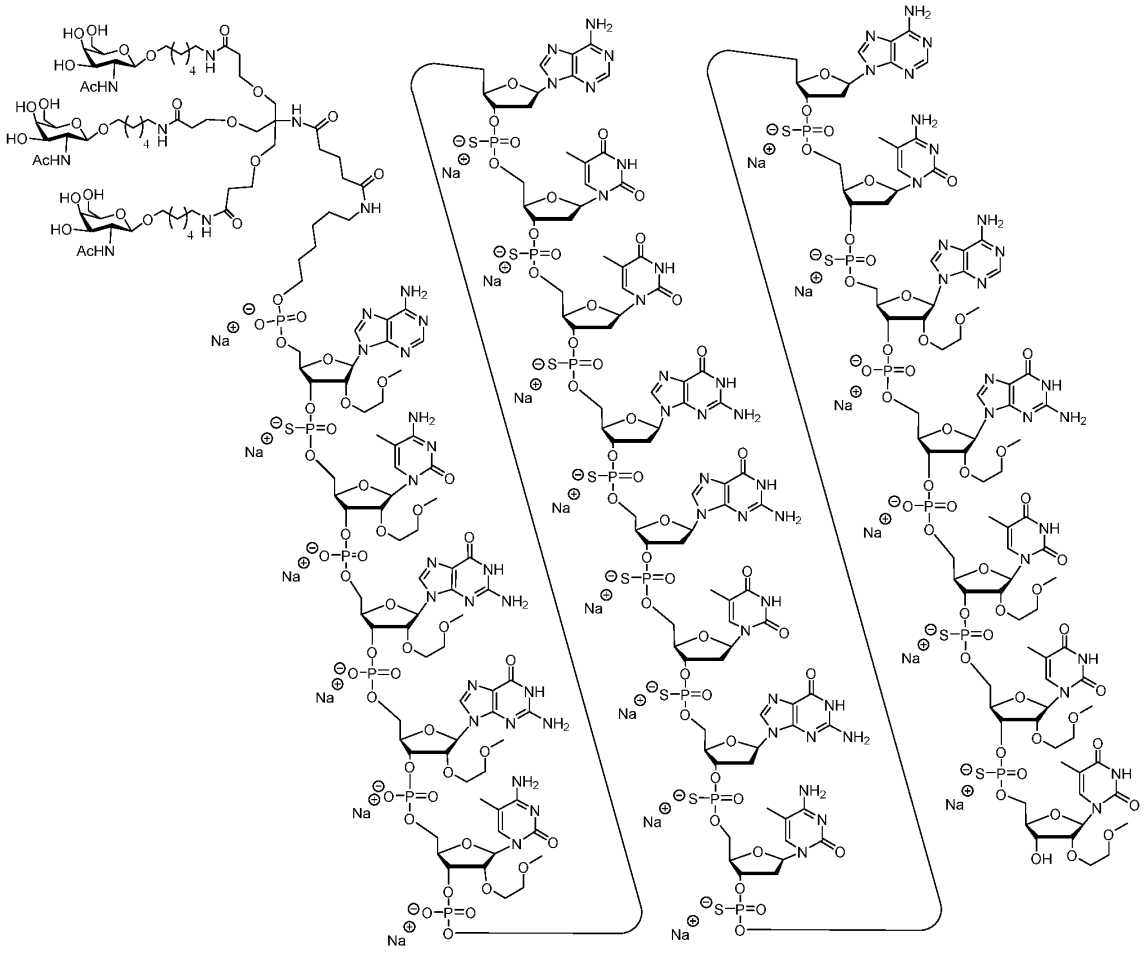
Embodiment 53. The method of any one of embodiments 27-52, wherein the animal has been identified as having a thromboembolic condition or has been identified as being at risk of having a thromboembolic condition.

Embodiment 54. The method of embodiment 53, further comprising identifying the animal as having the thromboembolic condition or at risk for having the thromboembolic condition.

Embodiment 55. The method of any one of embodiments 27-54, wherein the animal has been identified as having a disease selected from end stage renal disease (ESRD), chronic kidney disease (CKD), and coronary artery disease (CAD), or has been identified as being at risk for a disease selected from ESRD, CKD, and CAD.

Embodiment 56. The method of embodiment 55, further comprising identifying the animal as having the disease, or identifying the animal as being at risk for having the disease.

Embodiment 57. A method comprising administering a first dose and a second dose of an oligomeric compound according to the following formula:



(SEQ ID NO: 3)

wherein the first dose and the second dose are separated by 20 to 40 days, and wherein the oligomeric compound is in the form of a dosage unit consisting or consisting essentially of about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, or about 100 mg of the oligomeric compound and about 0.4 ml, about 0.5 ml, about 0.6 ml, about 0.7 ml, about 0.8 ml, about 0.9 ml, or about 1 ml of a pharmaceutically acceptable carrier or diluent.

Embodiment 58. The method of embodiment 57, wherein the first dose and the second dose are separated by 27 to 32 days, and wherein the dosage unit consists or consists essentially of 75 mg to 85 mg of the oligomeric compound and 0.7 ml to 0.9 ml of the pharmaceutically acceptable carrier or diluent.

Embodiment 59. The method of embodiment 57, wherein the dosage unit consists or consists essentially of about 80 mg of the oligomeric compound and about 0.8 ml of the pharmaceutically acceptable carrier or diluent.

Embodiment 60. A method comprising administering a dosage unit to an animal monthly, wherein the dosage unit consists or consists essentially of the oligomeric compound of any one of embodiments 1-5 and a pharmaceutically acceptable carrier or diluent, and wherein the concentration of the oligomeric compound is 80 mg/ml to 120 mg/ml.

Embodiment 61. A method comprising administering a dosage unit to an animal monthly, wherein the dosage unit consists or consists essentially of the oligomeric compound of any one of embodiments 1-5 and a pharmaceutically acceptable carrier or diluent, and wherein the concentration of the oligomeric compound is about 100 mg/ml.

Embodiment 62. The method of any one of embodiments 57 to 61, wherein the pharmaceutically acceptable carrier or diluent is phosphate buffered saline.

Embodiment 63. A lyophilized powder comprising the oligomeric compound of any one of claims 1-5.

I. Certain Oligonucleotides

In certain embodiments, provided herein are oligomeric compounds comprising oligonucleotides, which consist of linked nucleosides. Oligonucleotides may be unmodified oligonucleotides (RNA or DNA) or may be modified oligonucleotides. Modified oligonucleotides comprise at least one modification relative to unmodified RNA or DNA. That is, modified oligonucleotides comprise at least one modified nucleoside (comprising a modified sugar moiety and/or a modified nucleobase) and/or at least one modified internucleoside linkage.

A. Certain Modified Nucleosides

Modified nucleosides comprise a modified sugar moiety or a modified nucleobase or both a modifed sugar moiety and a modified nucleobase.

1. Certain Sugar Moieties

In certain embodiments, modified sugar moieties are non-bicyclic modified sugar moieties. In certain embodiments, modified sugar moieties are bicyclic or tricyclic sugar moieties. In certain embodiments, modified sugar moieties are sugar surrogates. Such sugar surrogates may comprise one or more substitutions corresponding to those of other types of modified sugar moieties.

In certain embodiments, modified sugar moieties are non-bicyclic modified sugar moieties comprising a furanosyl ring with one or more substituent groups none of which bridges two atoms of the furanosyl ring to form a bicyclic structure. Such non bridging substituents may be at any position of the furanosyl, including but not limited to substituents at the 2', 4', and/or 5' positions. In certain embodiments one or more non-bridging substituent of non-bicyclic modified sugar moieties is branched. Examples of 2'-substituent groups suitable for non-bicyclic modified sugar moieties include but are not limited to: 2'-F, 2'-OCH_3 ("OMe" or "O-methyl"), and 2'-$O(CH_2)_2OCH_3$ ("MOE"). In certain embodiments, 2'-substituent groups are selected from among: halo, allyl, amino, azido, SH, CN, OCN, CF_3, OCF_3, O-C_1-C_{10} alkoxy, O-

C_1-C_{10} substituted alkoxy, O-C_1-C_{10} alkyl, O-C_1-C_{10} substituted alkyl, S-alkyl, N(R_m)-alkyl, O-alkenyl, S-alkenyl, N(R_m)-alkenyl, O-alkynyl, S-alkynyl, N(R_m)-alkynyl, O-alkylenyl-O-alkyl, alkynyl, alkaryl, aralkyl, O-alkaryl, O-aralkyl, $O(CH_2)_2SCH_3$, $O(CH_2)_2ON(R_m)(R_n)$ or $OCH_2C(=O)$-$N(R_m)(R_n)$, where each R_m and R_n is, independently, H, an amino protecting group, or substituted or unsubstituted C_1-C_{10} alkyl, and the 2'-substituent groups described in Cook et al., U.S. 6,531,584; Cook et al., U.S. 5,859,221; and Cook et al., U.S. 6,005,087. Certain embodiments of these 2'-substituent groups can be further substituted with one or more substituent groups independently selected from among: hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro (NO_2), thiol, thioalkoxy, thioalkyl, halogen, alkyl, aryl, alkenyl and alkynyl. Examples of 4'-substituent groups suitable for non-bicyclic modified sugar moieties include but are not limited to alkoxy (*e.g.*, methoxy), alkyl, and those described in Manoharan et al., WO 2015/106128. Examples of 5'-substituent groups suitable for non-bicyclic modified sugar moieties include but are not limited to: 5'-methyl (R or S), 5'-vinyl, and 5'-methoxy. In certain embodiments, non-bicyclic modified sugar moieties comprise more than one non-bridging sugar substituent, for example, 2'-F-5'-methyl sugar moieties and the modified sugar moieties and modified nucleosides described in Migawa et al., WO 2008/101157 and Rajeev et al., US2013/0203836.).

In certain embodiments, a 2'-substituted non-bicyclic modified nucleoside comprises a sugar moiety comprising a non-bridging 2'-substituent group selected from: F, NH_2, N_3, OCF_3, OCH_3, $O(CH_2)_3NH_2$, $CH_2CH{=}CH_2$, $OCH_2CH{=}CH_2$, $OCH_2CH_2OCH_3$, $O(CH_2)_2SCH_3$, $O(CH_2)_2ON(R_m)(R_n)$, $O(CH_2)_2O(CH_2)_2N(CH_3)_2$, and N-substituted acetamide ($OCH_2C(=O)$-$N(R_m)(R_n)$), where each R_m and R_n is, independently, H, an amino protecting group, or substituted or unsubstituted C_1-C_{10} alkyl.

In certain embodiments, a 2'-substituted nucleoside non-bicyclic modified nucleoside comprises a sugar moiety comprising a non-bridging 2'-substituent group selected from: F, OCF_3, OCH_3, $OCH_2CH_2OCH_3$, $O(CH_2)_2SCH_3$, $O(CH_2)_2ON(CH_3)_2$, $O(CH_2)_2O(CH_2)_2N(CH_3)_2$, and $OCH_2C(=O)$-$N(H)CH_3$ ("NMA").

In certain embodiments, a 2'-substituted non-bicyclic modified nucleoside comprises a sugar moiety comprising a non-bridging 2'-substituent group selected from: F, OCH_3, and $OCH_2CH_2OCH_3$.

Certain modifed sugar moieties comprise a substituent that bridges two atoms of the furanosyl ring to form a second ring, resulting in a bicyclic sugar moiety. In certain such embodiments, the bicyclic sugar moiety comprises a bridge between the 4' and the 2' furanose ring atoms. Examples of such 4' to 2' bridging sugar substituents include but are not limited to: 4'-CH_2-2', 4'-$(CH_2)_2$-2', 4'-$(CH_2)_3$-2', 4'-CH_2-O-2' ("LNA"), 4'-CH_2-S-2', 4'-$(CH_2)_2$-O-2' ("ENA"), 4'-$CH(CH_3)$-O-2' (referred to as "constrained ethyl" or "cEt"), 4'-CH_2-O-CH_2-2', 4'-CH_2-N(R)-2', 4'-$CH(CH_2OCH_3)$-O-2' ("constrained MOE" or "cMOE") and analogs thereof (*see, e.g.,* Seth et al., U.S. 7,399,845, Bhat et al., U.S. 7,569,686, Swayze et al., U.S. 7,741,457, and Swayze et al., U.S. 8,022,193), 4'-$C(CH_3)(CH_3)$-O-2' and analogs thereof (*see, e.g.,* Seth et al., U.S. 8,278,283), 4'-CH_2-$N(OCH_3)$-2' and analogs thereof (*see, e.g.,* Prakash et al., U.S. 8,278,425), 4'-CH_2-O-$N(CH_3)$-2' (*see, e.g.,* Allerson et al., U.S. 7,696,345 and Allerson et al., U.S. 8,124,745), 4'-CH_2-$C(H)(CH_3)$-2' (*see, e.g.,*

Zhou, *et al., J. Org. Chem.,*2009, *74*, 118-134), 4'-CH_2-C(=CH_2)-2' and analogs thereof (*see e.g.*, Seth et al., U.S. 8,278,426), 4'C(-R_aR_b)-N(R)-O-2', 4'-C(R_aR_b)-O-N(R)-2', 4'-CH_2-O-N(R)-2', and 4'-CH_2-N(R)-O-2', wherein each R, R_a, and R_b is, independently, H, a protecting group, or C_1-C_{12} alkyl (*see, e.g.* Imanishi et al., U.S. 7,427,672).

In certain embodiments, such 4' to 2' bridges independently comprise from 1 to 4 linked groups independently selected from: -[C(R_a)(R_b)]$_n$-, -[C(R_a)(R_b)]$_n$-O-, -C(R_a)=C(R_b)-, -C(R_a)=N-, C(=-NR_a)-, -C(=O)-, -C(=S)-, -O-, -Si(R_a)$_2$-, -S(=O)$_x$-, and -N(R_a)-;

wherein:

x is 0, 1, or 2;

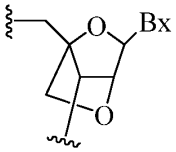
n is 1, 2, 3, or 4;

each R_a and R_b is, independently, H, a protecting group, hydroxyl, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, heterocycle radical, substituted heterocycle radical, heteroaryl, substituted heteroaryl, C_5-C_7 alicyclic radical, substituted C_5-C_7 alicyclic radical, halogen, OJ_1, NJ_1J_2, SJ_1, N_3, COOJ_1, acyl (C(=O)-H), substituted acyl, CN, sulfonyl (S(=O)$_2$-J_1), or sulfoxyl (S(=O)-J_1); and

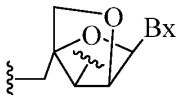
each J_1 and J_2 is, independently, H, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, acyl (C(=O)-H), substituted acyl, a heterocycle radical, a substituted heterocycle radical, C_1-C_{12} aminoalkyl, substituted C_1-C_{12} aminoalkyl, or a protecting group.

Additional bicyclic sugar moieties are known in the art, see, for example: Freier *et al., Nucleic Acids Research*, 1997, *25*(*22*), 4429-4443, Albaek *et al., J. Org. Chem.*, 2006, *71*, 7731-7740, Singh et al., *Chem. Commun.*, 1998, *4*, 455-456; Koshkin et al., *Tetrahedron*, 1998, *54*, 3607-3630; Kumar et al., *Bioorg. Med. Chem. Lett.*, 1998, *8*, 2219-2222; Singh et al., *J. Org. Chem.*, 1998, *63*, 10035-10039; Srivastava et al., *J. Am. Chem. Soc.*, 20017, *129,* 8362-8379;Wengel et a., U.S. 7,053,207; Imanishi et al., U.S. 6,268,490; Imanishi et al. U.S. 6,770,748; Imanishi et al., U.S. RE44,779; Wengel et al., U.S. 6,794,499; Wengel et al., U.S. 6,670,461; Wengel et al., U.S. 7,034,133; Wengel et al., U.S. 8,080,644; Wengel et al., U.S. 8,034,909; Wengel et al., U.S. 8,153,365; Wengel et al., U.S. 7,572,582; and Ramasamy et al., U.S. 6,525,191; Torsten et al., WO 2004/106356;Wengel et al., WO 1999/014226; Seth et al., WO 2007/134181; Seth et al., U.S. 7,547,684; Seth et al., U.S. 7,666,854; Seth et al., U.S. 8,088,746; Seth et al., U.S. 7,750,131; Seth et al., U.S. 8,030,467; Seth et al., U.S. 8,268,980; Seth et al., U.S. 8,546,556; Seth et al., U.S. 8,530,640; Migawa et al., U.S. 9,012,421; Seth et al., U.S. 8,501,805; and U.S. Patent Publication Nos. Allerson et al., US2008/0039618 and Migawa et al., US2015/0191727.

In certain embodiments, bicyclic sugar moieties and nucleosides incorporating such bicyclic sugar moieties are further defined by isomeric configuration. For example, an LNA nucleoside (described herein) may be in the α-L configuration or in the β-D configuration.



LNA (β-D-configuration)
bridge = 4'-CH_2-O-2'



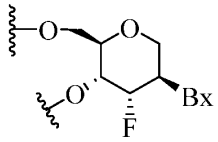
α-*L*-LNA (α-*L*-configuration)
bridge = 4'-CH_2-O-2'

α-L-methyleneoxy (4'-CH_2-O-2') or α-L-LNA bicyclic nucleosides have been incorporated into oligonucleotides that showed antisense activity (Frieden et al., *Nucleic Acids Research,* 2003, *21*, 6365-6372). Herein, general descriptions of bicyclic nucleosides include both isomeric configurations. When the positions of specific bicyclic nucleosides (*e.g.*, LNA or cEt) are identified in exemplified embodiments herein, they are in the β-D configuration, unless otherwise specified.

In certain embodiments, modified sugar moieties comprise one or more non-bridging sugar substituent and one or more bridging sugar substituent (*e.g.*, 5'-substituted and 4'-2' bridged sugars).

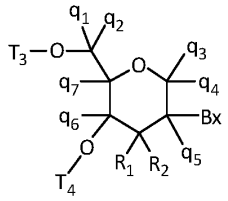
In certain embodiments, modified sugar moieties are sugar surrogates. In certain such embodiments, the oxygen atom of the sugar moiety is replaced, *e.g.,* with a sulfur, carbon or nitrogen atom. In certain such embodiments, such modified sugar moieties also comprise bridging and/or non-bridging substituents as described herein. For example, certain sugar surrogates comprise a 4'-sulfur atom and a substitution at the 2'-position (*see*, *e.g.,* Bhat et al., U.S. 7,875,733 and Bhat et al., U.S. 7,939,677) and/or the 5' position.

In certain embodiments, sugar surrogates comprise rings having other than 5 atoms. For example, in certain embodiments, a sugar surrogate comprises a six-membered tetrahydropyran ("THP"). Such tetrahydropyrans may be further modified or substituted. Nucleosides comprising such modified tetrahydropyrans include but are not limited to hexitol nucleic acid ("HNA"), anitol nucleic acid ("ANA"), manitol nucleic acid ("MNA") (*see, e.g.,* Leumann, CJ. *Bioorg. & Med. Chem.* 2002, *10*, 841-854), fluoro HNA:



F-HNA

("F-HNA", *see e.g.,* Swayze et al., U.S. 8,088,904; Swayze et al., U.S. 8,440,803; Swayze et al., U.S. 8,796,437; and Swayze et al., U.S. 9,005,906; F-HNA can also be referred to as a F-THP or 3'-fluoro tetrahydropyran), and nucleosides comprising additional modified THP compounds having the formula:



wherein, independently, for each of said modified THP nucleoside:

Bx is a nucleobase moiety;

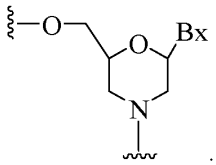
T_3 and T_4 are each, independently, an internucleoside linking group linking the modified THP nucleoside to the remainder of an oligonucleotide or one of T_3 and T_4 is an internucleoside linking group linking the modified THP nucleoside to the remainder of an oligonucleotide and the other of T_3 and T_4 is H, a hydroxyl protecting group, a linked conjugate group, or a 5' or 3'-terminal group;

q_1, q_2, q_3, q_4, q_5, q_6 and q_7 are each, independently, H, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_2-C_6 alkenyl, substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, or substituted C_2-C_6 alkynyl; and

each of R_1 and R_2 is independently selected from among: hydrogen, halogen, substituted or unsubstituted alkoxy, NJ_1J_2, SJ_1, N_3, $OC(=X)J_1$, $OC(=X)NJ_1J_2$, $NJ_3C(=X)NJ_1J_2$, and CN, wherein X is O, S or NJ_1, and each J_1, J_2, and J_3 is, independently, H or C_1-C_6 alkyl.

In certain embodiments, modified THP nucleosides are provided wherein q_1, q_2, q_3, q_4, q_5, q_6 and q_7 are each H. In certain embodiments, at least one of q_1, q_2, q_3, q_4, q_5, q_6 and q_7 is other than H. In certain embodiments, at least one of q_1, q_2, q_3, q_4, q_5, q_6 and q_7 is methyl. In certain embodiments, modified THP nucleosides are provided wherein one of R_1 and R_2 is F. In certain embodiments, R_1 is F and R_2 is H, in certain embodiments, R_1 is methoxy and R_2 is H, and in certain embodiments, R_1 is methoxyethoxy and R_2 is H.

In certain embodiments, sugar surrogates comprise rings having more than 5 atoms and more than one heteroatom. For example, nucleosides comprising morpholino sugar moieties and their use in oligonucleotides have been reported (*see, e.g.,* Braasch et al., Biochemistry, 2002, *41*, 4503-4510 and Summerton et al., U.S. 5,698,685; Summerton et al., U.S. 5,166,315; Summerton et al., U.S. 5,185,444; and Summerton et al., U.S. 5,034,506). As used here, the term "morpholino" means a sugar surrogate having the following structure:



In certain embodiments, morpholinos may be modified, for example by adding or altering various substituent groups from the above morpholino structure. Such sugar surrogates are referred to herein as "modifed morpholinos."

In certain embodiments, sugar surrogates comprise acyclic moieites. Examples of nucleosides and oligonucleotides comprising such acyclic sugar surrogates include but are not limited to: peptide nucleic acid ("PNA"), acyclic butyl nucleic acid (*see, e.g.,* Kumar et al., *Org. Biomol. Chem.*, 2013, *11*, 5853-5865), and nucleosides and oligonucleotides described in Manoharan et al., WO2011/133876.

Many other bicyclic and tricyclic sugar and sugar surrogate ring systems are known in the art that can be used in modified nucleosides (see for example review article: Leumann, Bioorg. Med. Chem., 2002, 10, 841-854).

2. Certain Modified Nucleobases

In certain embodiments, modified oligonucleotides comprise one or more nucleosides comprising an unmodified nucleobase. In certain embodiments, modified oligonucleotides comprise one or more nucleoside comprising a modified nucleobase. In certain embodiments, modified oligonucleotides comprise one or more nucleoside that does not comprise a nucleobase, referred to as an abasic nucleoside.

In certain embodiments, modified nucleobases are selected from: 5-substituted pyrimidines, 6-azapyrimidines, alkyl or alkynyl substituted pyrimidines, alkyl substituted purines, and N-2, N-6 and O-6 substituted purines. In certain embodiments, modified nucleobases are selected from: 2-aminopropyladenine, 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-N-methylguanine, 6-N-methyladenine, 2-propyladenine , 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-propynyl (-C≡C-CH_3) uracil, 5-propynylcytosine, 6-azouracil, 6-azocytosine, 6-azothymine, 5-ribosyluracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl, 8-aza and other 8-substituted purines, 5-halo, particularly 5-bromo, 5-trifluoromethyl, 5-halouracil, and 5-halocytosine, 7-methylguanine, 7-methyladenine, 2-F-adenine, 2-aminoadenine, 7-deazaguanine, 7-deazaadenine, 3-deazaguanine, 3-deazaadenine, 6-N-benzoyladenine, 2-N-isobutyrylguanine, 4-N-benzoylcytosine, 4-N-benzoyluracil, 5-methyl 4-N-benzoylcytosine, 5-methyl 4-N-benzoyluracil, universal bases, hydrophobic bases, promiscuous bases, size-expanded bases, and fluorinated bases. Further modified nucleobases include tricyclic pyrimidines, such as 1,3-diazaphenoxazine-2-one, 1,3-diazaphenothiazine-2-one and 9-(2-aminoethoxy)-1,3-diazaphenoxazine-2-one (G-clamp). Modified nucleobases may also include those in which the purine or pyrimidine base is replaced with other heterocycles, for example 7-deaza-adenine, 7-deazaguanosine, 2-aminopyridine and 2-pyridone. Further nucleobases include those disclosed in Merigan et al., U.S. 3,687,808, those disclosed in *The Concise Encyclopedia Of Polymer Science And Engineering*, Kroschwitz, J.I., Ed., John Wiley & Sons, 1990, 858-859; Englisch *et al.*, *Angewandte Chemie*, International Edition, 1991, *30*, 613; Sanghvi, Y.S., Chapter 15, *Antisense Research and Applications*, Crooke, S.T. and Lebleu, B., Eds., CRC Press, 1993, 273-288; and those disclosed in Chapters 6 and 15, *Antisense Drug Technology*, Crooke S.T., Ed., CRC Press, 2008, 163-166 and 442-443.

Publications that teach the preparation of certain of the above noted modified nucleobases as well as other modified nucleobases include without limitation, Manoharan et al., US2003/0158403; Manoharan et al., US2003/0175906; Dinh et al., U.S. 4,845,205; Spielvogel et al., U.S. 5,130,302; Rogers et al., U.S.

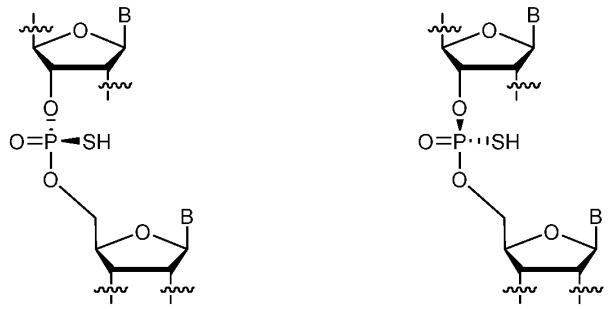
5,134,066; Bischofberger et al., U.S. 5,175,273; Urdea et al., U.S. 5,367,066; Benner et al., U.S. 5,432,272; Matteucci et al., U.S. 5,434,257; Gmeiner et al., U.S. 5,457,187; Cook et al., U.S. 5,459,255; Froehler et al., U.S. 5,484,908; Matteucci et al., U.S. 5,502,177; Hawkins et al., U.S. 5,525,711; Haralambidis et al., U.S. 5,552,540; Cook et al., U.S. 5,587,469; Froehler et al., U.S. 5,594,121; Switzer et al., U.S. 5,596,091; Cook et al., U.S. 5,614,617; Froehler et al., U.S. 5,645,985; Cook et al., U.S. 5,681,941; Cook et al., U.S. 5,811,534; Cook et al., U.S. 5,750,692; Cook et al., U.S. 5,948,903; Cook et al., U.S. 5,587,470; Cook et al., U.S. 5,457,191; Matteucci et al., U.S. 5,763,588; Froehler et al., U.S. 5,830,653; Cook et al., U.S. 5,808,027; Cook et al., 6,166,199; and Matteucci et al., U.S. 6,005,096.

3. Certain Modified Internucleoside Linkages

In certain embodiments, nucleosides of modified oligonucleotides may be linked together using any internucleoside linkage. The two main classes of internucleoside linking groups are defined by the presence or absence of a phosphorus atom. Representative phosphorus-containing internucleoside linkages include but are not limited to phosphodiesters ("P=O") (also referred to as unmodified or naturally occurring linkages or phosphate linkages), phosphotriesters, methylphosphonates, phosphoramidates, and phosphorothioates ("P=S"), and phosphorodithioates ("HS-P=S"). Representative non-phosphorus containing internucleoside linking groups include but are not limited to methylenemethylimino ($-CH_2-N(CH_3)-O-CH_2-$), thiodiester, thionocarbamate (-O-C(=O)(NH)-S-); siloxane ($-O-SiH_2-O-$); and N,N'-dimethylhydrazine ($-CH_2-N(CH_3)-N(CH_3)-$). Modified internucleoside linkages, compared to naturally occurring phosphodiester linkages, can be used to alter, typically increase, nuclease resistance of the oligonucleotide. In certain embodiments, internucleoside linkages having a chiral atom can be prepared as a racemic mixture, or as separate enantiomers. Methods of preparation of phosphorous-containing and non-phosphorous-containing internucleoside linkages are well known to those skilled in the art.

Representative internucleoside linkages having a chiral center include but are not limited to alkylphosphonates and phosphorothioates. Modified oligonucleotides comprising internucleoside linkages having a chiral center can be prepared as populations of modified oligonucleotides comprising stereorandom internucleoside linkages, or as populations of modified oligonucleotides comprising phosphorothioate linkages in particular stereochemical configurations. In certain embodiments, populations of modified oligonucleotides comprise phosphorothioate internucleoside linkages wherein all of the phosphorothioate internucleoside linkages are stereorandom. Such modified oligonucleotides can be generated using synthetic methods that result in random selection of the stereochemical configuration of each phosphorothioate linkage. Nonetheless, as is well understood by those of skill in the art, each individual phosphorothioate of each individual oligonucleotide molecule has a defined stereoconfiguration. In certain embodiments, populations of modified oligonucleotides are enriched for modified oligonucleotides comprising one or more particular phosphorothioate internucleoside linkages in a particular, independently selected stereochemical configuration. In certain embodiments, the particular configuration of the particular phosphorothioate linkage is present in at least 65% of the molecules in the population. In certain embodiments, the particular

configuration of the particular phosphorothioate linkage is present in at least 70% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate linkage is present in at least 80% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate linkage is present in at least 90% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate linkage is present in at least 99% of the molecules in the population. Such chirally enriched populations of modified oligonucleotides can be generated using synthetic methods known in the art, *e.g.*, methods described in Oka et al., *JACS* 125, 8307 (2003), Wan et al. *Nuc. Acid. Res.* 42, 13456 (2014), and WO 2017/015555. In certain embodiments, a population of modified oligonucleotides is enriched for modified oligonucleotides having at least one indicated phosphorothioate in the (*S*p) configuration. In certain embodiments, a population of modified oligonucleotides is enriched for modified oligonucleotides having at least one phosphorothioate in the (*R*p) configuration. In certain embodiments, modified oligonucleotides comprising (*R*p) and/or (*S*p) phosphorothioates comprise one or more of the following formulas, respectively, wherein "B" indicates a nucleobase:



Unless otherwise indicated, chiral internucleoside linkages of modified oligonucleotides described herein can be stereorandom or in a particular stereochemical configuration.

Neutral internucleoside linkages include, without limitation, phosphotriesters, methylphosphonates, MMI (3'-CH_2-N(CH_3)-O-5'), amide-3 (3'-CH_2-C(=O)-N(H)-5'), amide-4 (3'-CH_2-N(H)-C(=O)-5'), formacetal (3'-O-CH_2-O-5'), methoxypropyl, and thioformacetal (3'-S-CH_2-O-5'). Further neutral internucleoside linkages include nonionic linkages comprising siloxane (dialkylsiloxane), carboxylate ester, carboxamide, sulfide, sulfonate ester and amides (See for example: *Carbohydrate Modifications in Antisense Research*; Y.S. Sanghvi and P.D. Cook, Eds., ACS Symposium Series 580; Chapters 3 and 4, 40-65). Further neutral internucleoside linkages include nonionic linkages comprising mixed N, O, S and CH_2 component parts.

B. Certain Motifs

In certain embodiments, modified oligonucleotides comprise one or more modified nucleosides comprising a modified sugar moiety. In certain embodiments, modified oligonucleotides comprise one or more modified nucleosides comprising a modified nucleobase. In certain embodiments, modified

oligonucleotides comprise one or more modified internucleoside linkage. In such embodiments, the modified, unmodified, and differently modified sugar moieties, nucleobases, and/or internucleoside linkages of a modified oligonucleotide define a pattern or motif. In certain embodiments, the patterns of sugar moieties, nucleobases, and internucleoside linkages are each independent of one another. Thus, a modified oligonucleotide may be described by its sugar motif, nucleobase motif and/or internucleoside linkage motif (as used herein, nucleobase motif describes the modifications to the nucleobases independent of the sequence of nucleobases).

1. **Certain Sugar Motifs**

In certain embodiments, oligonucleotides comprise one or more type of modified sugar and/or unmodified sugar moiety arranged along the oligonucleotide or region thereof in a defined pattern or sugar motif. In certain instances, such sugar motifs include but are not limited to any of the sugar modifications discussed herein.

In certain embodiments, modified oligonucleotides comprise or consist of a region having a gapmer motif, which is defined by two external regions or "wings" and a central or internal region or "gap." The three regions of a gapmer motif (the 5'-wing, the gap, and the 3'-wing) form a contiguous sequence of nucleosides wherein at least some of the sugar moieties of the nucleosides of each of the wings differ from at least some of the sugar moieties of the nucleosides of the gap. Specifically, at least the sugar moieties of the nucleosides of each wing that are closest to the gap (the 3'-most nucleoside of the 5'-wing and the 5'-most nucleoside of the 3'-wing) differ from the sugar moiety of the neighboring gap nucleosides, thus defining the boundary between the wings and the gap (i.e., the wing/gap junction). In certain embodiments, the sugar moieties within the gap are the same as one another. In certain embodiments, the gap includes one or more nucleoside having a sugar moiety that differs from the sugar moiety of one or more other nucleosides of the gap. In certain embodiments, the sugar motifs of the two wings are the same as one another (symmetric gapmer). In certain embodiments, the sugar motif of the 5'-wing differs from the sugar motif of the 3'-wing (asymmetric gapmer).

In certain embodiments, the wings of a gapmer comprise 1-5 nucleosides. In certain embodiments, each nucleoside of each wing of a gapmer is a modified nucleoside. In certain embodiments, at least one nucleoside of each wing of a gapmer is a modified nucleoside. In certain embodiments, at least two nucleosides of each wing of a gapmer are modified nucleosides. In certain embodiments, at least three nucleosides of each wing of a gapmer are modified nucleosides. In certain embodiments, at least four nucleosides of each wing of a gapmer are modified nucleosides.

In certain embodiments, the gap of a gapmer comprises 7-12 nucleosides. In certain embodiments, each nucleoside of the gap of a gapmer is an unmodified 2'-deoxy nucleoside.

In certain embodiments, the gapmer is a deoxy gapmer. In embodiments, the nucleosides on the gap side of each wing/gap junction are unmodified 2'-deoxy nucleosides and the nucleosides on the wing sides of each wing/gap junction are modified nucleosides. In certain embodiments, each nucleoside of the gap is an

unmodified 2'-deoxy nucleoside. In certain embodiments, each nucleoside of each wing of a gapmer is a modified nucleoside.

In certain embodiments, modified oligonucleotides comprise or consist of a region having a fully modified sugar motif. In such embodiments, each nucleoside of the fully modified region of the modified oligonucleotide comprises a modified sugar moiety. In certain embodiments, each nucleoside of the entire modified oligonucleotide comprises a modified sugar moiety. In certain embodiments, modified oligonucleotides comprise or consist of a region having a fully modified sugar motif, wherein each nucleoside within the fully modified region comprises the same modified sugar moiety, referred to herein as a uniformly modified sugar motif. In certain embodiments, a fully modified oligonucleotide is a uniformly modified oligonucleotide. In certain embodiments, each nucleoside of a uniformly modified comprises the same 2'-modification.

Herein, the lengths (number of nucleosides) of the three regions of a gapmer may be provided using the notation [# of nucleosides in the 5'-wing] – [# of nucleosides in the gap] – [# of nucleosides in the 3'-wing]. Thus, a 5-10-5 gapmer consists of 5 linked nucleosides in each wing and 10 linked nucleosides in the gap. Where such nomenclature is followed by a specific modification, that modification is the modification in each sugar moiety of each wing and the gap nucleosides comprise unmodified deoxynucleoside sugars. Thus, a 5-10-5 MOE gapmer consists of 5 linked MOE modified nucleosides in the 5'-wing, 10 linked deoxynucleosides in the gap, and 5 linked MOE nucleosides in the 3'-wing.

In certain embodiments, modified oligonucleotides are 5-10-5 MOE gapmers. In certain embodiments, modified oligonucleotides are 3-10-3 BNA gapmers. In certain embodiments, modified oligonucleotides are 3-10-3 cEt gapmers. In certain embodiments, modified oligonucleotides are 3-10-3 LNA gapmers.

2. Certain Nucleobase Motifs

In certain embodiments, oligonucleotides comprise modified and/or unmodified nucleobases arranged along the oligonucleotide or region thereof in a defined pattern or motif. In certain embodiments, each nucleobase is modified. In certain embodiments, none of the nucleobases are modified. In certain embodiments, each purine or each pyrimidine is modified. In certain embodiments, each adenine is modified. In certain embodiments, each guanine is modified. In certain embodiments, each thymine is modified. In certain embodiments, each uracil is modified. In certain embodiments, each cytosine is modified. In certain embodiments, some or all of the cytosine nucleobases in a modified oligonucleotide are 5-methyl cytosines. In certain embodiments, all of the cytosine nucleobases are 5-methyl cytosines and all of the other nucleobases of the modified oligonucleotide are unmodified nucleobases.

In certain embodiments, modified oligonucleotides comprise a block of modified nucleobases. In certain such embodiments, the block is at the 3'-end of the oligonucleotide. In certain embodiments the block is within 3 nucleosides of the 3'-end of the oligonucleotide. In certain embodiments, the block is at the 5'-

end of the oligonucleotide. In certain embodiments the block is within 3 nucleosides of the 5'-end of the oligonucleotide.

In certain embodiments, oligonucleotides having a gapmer motif comprise a nucleoside comprising a modified nucleobase. In certain such embodiments, one nucleoside comprising a modified nucleobase is in the central gap of an oligonucleotide having a gapmer motif. In certain such embodiments, the sugar moiety of said nucleoside is a 2'-deoxyribosyl moiety. In certain embodiments, the modified nucleobase is selected from: a 2-thiopyrimidine and a 5-propynepyrimidine.

3. Certain Internucleoside Linkage Motifs

In certain embodiments, oligonucleotides comprise modified and/or unmodified internucleoside linkages arranged along the oligonucleotide or region thereof in a defined pattern or motif. In certain embodiments, each internucleoside linking group is a phosphodiester internucleoside linkage (P=O). In certain embodiments, each internucleoside linking group of a modified oligonucleotide is a phosphorothioate internucleoside linkage (P=S). In certain embodiments, each internucleoside linkage of a modified oligonucleotide is independently selected from a phosphorothioate internucleoside linkage and phosphodiester internucleoside linkage. In certain embodiments, each phosphorothioate internucleoside linkage is independently selected from a stereorandom phosphorothioate, a (*S*p) phosphorothioate, and a (*R*p) phosphorothioate. In certain embodiments, the sugar motif of a modified oligonucleotide is a gapmer and the internucleoside linkages within the gap are all modified. In certain such embodiments, some or all of the internucleoside linkages in the wings are unmodified phosphodiester internucleoside linkages. In certain embodiments, the terminal internucleoside linkages are modified. In certain embodiments, the sugar motif of a modified oligonucleotide is a gapmer, and the internucleoside linkage motif comprises at least one phosphodiester internucleoside linkage in at least one wing, wherein the at least one phosphodiester linkage is not a terminal internucleoside linkage, and the remaining internucleoside linkages are phosphorothioate internucleoside linkages. In certain such embodiments, all of the phosphorothioate linkages are stereorandom. In certain embodiments, all of the phosphorothioate linkages in the wings are (Sp) phosphorothioates, and the gap comprises at least one Sp, Sp, Rp motif. In certain embodiments, populations of modified oligonucleotides are enriched for modified oligonucleotides comprising such internucleoside linkage motifs.

C. Certain Lengths

It is possible to increase or decrease the length of an oligonucleotide without eliminating activity. For example, in Woolf et al. (Proc. Natl. Acad. Sci. USA 89:7305-7309, 1992), a series of oligonucleotides 13-25 nucleobases in length were tested for their ability to induce cleavage of a target RNA in an oocyte injection model. Oligonucleotides 25 nucleobases in length with 8 or 11 mismatch bases near the ends of the oligonucleotides were able to direct specific cleavage of the target RNA, albeit to a lesser extent than the oligonucleotides that contained no mismatches. Similarly, target specific cleavage was achieved using 13 nucleobase oligonucleotides, including those with 1 or 3 mismatches.

In certain embodiments, oligonucleotides (including modified oligonucleotides) can have any of a

variety of ranges of lengths. In certain embodiments, oligonucleotides consist of X to Y linked nucleosides, where X represents the fewest number of nucleosides in the range and Y represents the largest number nucleosides in the range. In certain such embodiments, X and Y are each independently selected from 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, and 50; provided that X≤Y. For example, in certain embodiments, oligonucleotides consist of 12 to 13, 12 to 14, 12 to 15, 12 to 16, 12 to 17, 12 to 18, 12 to 19, 12 to 20, 12 to 21, 12 to 22, 12 to 23, 12 to 24, 12 to 25, 12 to 26, 12 to 27, 12 to 28, 12 to 29, 12 to 30, 13 to 14, 13 to 15, 13 to 16, 13 to 17, 13 to 18, 13 to 19, 13 to 20, 13 to 21, 13 to 22, 13 to 23, 13 to 24, 13 to 25, 13 to 26, 13 to 27, 13 to 28, 13 to 29, 13 to 30, 14 to 15, 14 to 16, 14 to 17, 14 to 18, 14 to 19, 14 to 20, 14 to 21, 14 to 22, 14 to 23, 14 to 24, 14 to 25, 14 to 26, 14 to 27, 14 to 28, 14 to 29, 14 to 30, 15 to 16, 15 to 17, 15 to 18, 15 to 19, 15 to 20, 15 to 21, 15 to 22, 15 to 23, 15 to 24, 15 to 25, 15 to 26, 15 to 27, 15 to 28, 15 to 29, 15 to 30, 16 to 17, 16 to 18, 16 to 19, 16 to 20, 16 to 21, 16 to 22, 16 to 23, 16 to 24, 16 to 25, 16 to 26, 16 to 27, 16 to 28, 16 to 29, 16 to 30, 17 to 18, 17 to 19, 17 to 20, 17 to 21, 17 to 22, 17 to 23, 17 to 24, 17 to 25, 17 to 26, 17 to 27, 17 to 28, 17 to 29, 17 to 30, 18 to 19, 18 to 20, 18 to 21, 18 to 22, 18 to 23, 18 to 24, 18 to 25, 18 to 26, 18 to 27, 18 to 28, 18 to 29, 18 to 30, 19 to 20, 19 to 21, 19 to 22, 19 to 23, 19 to 24, 19 to 25, 19 to 26, 19 to 29, 19 to 28, 19 to 29, 19 to 30, 20 to 21, 20 to 22, 20 to 23, 20 to 24, 20 to 25, 20 to 26, 20 to 27, 20 to 28, 20 to 29, 20 to 30, 21 to 22, 21 to 23, 21 to 24, 21 to 25, 21 to 26, 21 to 27, 21 to 28, 21 to 29, 21 to 30, 22 to 23, 22 to 24, 22 to 25, 22 to 26, 22 to 27, 22 to 28, 22 to 29, 22 to 30, 23 to 24, 23 to 25, 23 to 26, 23 to 27, 23 to 28, 23 to 29, 23 to 30, 24 to 25, 24 to 26, 24 to 27, 24 to 28, 24 to 29, 24 to 30, 25 to 26, 25 to 27, 25 to 28, 25 to 29, 25 to 30, 26 to 27, 26 to 28, 26 to 29, 26 to 30, 27 to 28, 27 to 29, 27 to 30, 28 to 29, 28 to 30, or 29 to 30 linked nucleosides

D. Certain Modified Oligonucleotides

In certain embodiments, the above modifications (sugar, nucleobase, internucleoside linkage) are incorporated into a modified oligonucleotide. In certain embodiments, modified oligonucleotides are characterized by their modification motifs and overall lengths. In certain embodiments, such parameters are each independent of one another. Thus, unless otherwise indicated, each internucleoside linkage of an oligonucleotide having a gapmer sugar motif may be modified or unmodified and may or may not follow the gapmer modification pattern of the sugar modifications. For example, the internucleoside linkages within the wing regions of a sugar gapmer may be the same or different from one another and may be the same or different from the internucleoside linkages of the gap region of the sugar motif. Likewise, such sugar gapmer oligonucleotides may comprise one or more modified nucleobase independent of the gapmer pattern of the sugar modifications. Unless otherwise indicated, all modifications are independent of nucleobase sequence.

E. Certain Populations of Modified Oligonucleotides

Populations of modified oligonucleotides in which all of the modified oligonucleotides of the population have the same molecular formula can be stereorandom populations or chirally enriched populations. All of the chiral centers of all of the modified oligonucleotides are stereorandom in a stereorandom population. In a

chirally enriched population, at least one particular chiral center is not stereorandom in the modified oligonucleotides of the population. In certain embodiments, the modified oligonucleotides of a chirally enriched population are enriched for β-D ribosyl sugar moieties, and all of the phosphorothioate internucleoside linkages are stereorandom. In certain embodiments, the modified oligonucleotides of a chirally enriched population are enriched for both β-D ribosyl sugar moieties and at least one, particular phosphorothioate internucleoside linkage in a particular stereochemical configuration.

F. Nucleobase Sequence

In certain embodiments, oligonucleotides (unmodified or modified oligonucleotides) are further described by their nucleobase sequence. In certain embodiments oligonucleotides have a nucleobase sequence that is complementary to a second oligonucleotide or an identified reference nucleic acid, such as a target nucleic acid. In certain such embodiments, a region of an oligonucleotide has a nucleobase sequence that is complementary to a second oligonucleotide or an identified reference nucleic acid, such as a target nucleic acid. In certain embodiments, the nucleobase sequence of a region or entire length of an oligonucleotide is at least 50%, at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 95%, or 100% complementary to the second oligonucleotide or nucleic acid, such as a target nucleic acid.

II. Certain Oligomeric Compounds

In certain embodiments, provided herein are oligomeric compounds, which consist of an oligonucleotide (modified or unmodified) and optionally one or more conjugate groups and/or terminal groups. Conjugate groups consist of one or more conjugate moieties and a conjugate linker which links the conjugate moiety to the oligonucleotide. Conjugate groups may be attached to either or both ends of an oligonucleotide and/or at any internal position. In certain embodiments, conjugate groups are attached to the 2'-position of a nucleoside of a modified oligonucleotide. In certain embodiments, conjugate groups are attached to the 3' and/or 5' end of oligonucleotides. In certain embodiments, conjugate groups that are attached to either or both ends of an oligonucleotide are terminal groups. In certain such embodiments, conjugate groups (or terminal groups) are attached at the 3'-end of oligonucleotides. In certain embodiments, conjugate groups are attached near the 3'-end of oligonucleotides. In certain embodiments, conjugate groups (or terminal groups) are attached at the 5'-end of oligonucleotides. In certain embodiments, conjugate groups are attached near the 5'-end of oligonucleotides.

Examples of terminal groups include but are not limited to conjugate groups, capping groups, phosphate moieties, protecting groups, modified or unmodified nucleosides, and two or more nucleosides that are independently modified or unmodified.

A. Certain Conjugate Groups

In certain embodiments, oligonucleotides are covalently attached to one or more conjugate groups. In certain embodiments, conjugate groups modify one or more properties of the attached oligonucleotide, including but not limited to pharmacodynamics, pharmacokinetics, stability, binding, absorption, tissue distribution, cellular distribution, cellular uptake, charge and clearance. In certain embodiments, conjugate

groups impart a new property on the attached oligonucleotide, *e.g.*, fluorophores or reporter groups that enable detection of the oligonucleotide. Certain conjugate groups and conjugate moieties have been described previously, for example: cholesterol moiety (Letsinger et al., Proc. Natl. Acad. Sci. USA, 1989, 86, 6553-6556), cholic acid (Manoharan et al., *Bioorg. Med. Chem. Lett.*, 1994, *4*, 1053-1060), a thioether, *e.g.*, hexyl-S-tritylthiol (Manoharan et al., *Ann. N.Y. Acad. Sci.*, 1992, *660*, 306-309; Manoharan et al., *Bioorg. Med. Chem. Lett.*, 1993, *3*, 2765-2770), a thiocholesterol (Oberhauser et al., *Nucl. Acids Res.*, 1992, *20*, 533-538), an aliphatic chain, *e.g.*, do-decan-diol or undecyl residues (Saison-Behmoaras et al., *EMBO J.*, 1991, *10*, 1111-1118; Kabanov et al., *FEBS Lett.*, 1990, *259*, 327-330; Svinarchuk et al., *Biochimie*, 1993, *75*, 49-54), a phospholipid, *e.g.*, di-hexadecyl-rac-glycerol or triethyl-ammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate (Manoharan et al., *Tetrahedron Lett.*, 1995, *36*, 3651-3654; Shea et al., *Nucl. Acids Res.*, 1990, *18*, 3777-3783), a polyamine or a polyethylene glycol chain (Manoharan et al., *Nucleosides & Nucleotides*, 1995, *14*, 969-973), or adamantane acetic acid a palmityl moiety (Mishra et al., *Biochim. Biophys. Acta*, 1995, *1264*, 229-237), an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety (Crooke et al., *J. Pharmacol. Exp. Ther.*, 1996, *277*, 923-937), a tocopherol group (Nishina et al., *Molecular Therapy Nucleic Acids*, 2015, *4*, e220; and Nishina et al., *Molecular Therapy*, 2008, *16*, 734-740), or a GalNAc cluster (*e.g.*, WO2014/179620).

1. **Conjugate Moieties**

Conjugate moieties include, without limitation, intercalators, reporter molecules, polyamines, polyamides, peptides, carbohydrates, vitamin moieties, polyethylene glycols, thioethers, polyethers, cholesterols, thiocholesterols, cholic acid moieties, folate, lipids, phospholipids, biotin, phenazine, phenanthridine, anthraquinone, adamantane, acridine, fluoresceins, rhodamines, coumarins, fluorophores, and dyes.

In certain embodiments, a conjugate moiety comprises an active drug substance, for example, aspirin, warfarin, phenylbutazone, ibuprofen, suprofen, fen-bufen, ketoprofen, (*S*)-(+)-pranoprofen, carprofen, dansylsarcosine, 2,3,5-triiodobenzoic acid, fingolimod, flufenamic acid, folinic acid, a benzothiadiazide, chlorothiazide, a diazepine, indo-methicin, a barbiturate, a cephalosporin, a sulfa drug, an antidiabetic, an antibacterial or an antibiotic.

2. **Conjugate Linkers**

Conjugate moieties are attached to oligonucleotides through conjugate linkers. In certain oligomeric compounds, the conjugate linker is a single chemical bond (i.e., the conjugate moiety is attached directly to an oligonucleotide through a single bond). In certain embodiments, the conjugate linker comprises a chain structure, such as a hydrocarbyl chain, or an oligomer of repeating units such as ethylene glycol, nucleosides, or amino acid units.

In certain embodiments, a conjugate linker comprises one or more groups selected from alkyl, amino, oxo, amide, disulfide, polyethylene glycol, ether, thioether, and hydroxylamino. In certain such embodiments, the conjugate linker comprises groups selected from alkyl, amino, oxo, amide and ether groups. In certain

embodiments, the conjugate linker comprises groups selected from alkyl and amide groups. In certain embodiments, the conjugate linker comprises groups selected from alkyl and ether groups. In certain embodiments, the conjugate linker comprises at least one phosphorus moiety. In certain embodiments, the conjugate linker comprises at least one phosphate group. In certain embodiments, the conjugate linker includes at least one neutral linking group.

In certain embodiments, conjugate linkers, including the conjugate linkers described above, are bifunctional linking moieties, *e.g.,* those known in the art to be useful for attaching conjugate groups to parent compounds, such as the oligonucleotides provided herein. In general, a bifunctional linking moiety comprises at least two functional groups. One of the functional groups is selected to react with particular site on a parent compound and the other is selected to react with a conjugate group. Examples of functional groups used in a bifunctional linking moiety include but are not limited to electrophiles for reacting with nucleophilic groups and nucleophiles for reacting with electrophilic groups. In certain embodiments, bifunctional linking moieties comprise one or more groups selected from amino, hydroxyl, carboxylic acid, thiol, alkyl, alkenyl, and alkynyl.

Examples of conjugate linkers include but are not limited to pyrrolidine, 8-amino-3,6-dioxaoctanoic acid (ADO), succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC) and 6-aminohexanoic acid (AHEX or AHA). Other conjugate linkers include but are not limited to substituted or unsubstituted C_1-C_{10} alkyl, substituted or unsubstituted C_2-C_{10} alkenyl or substituted or unsubstituted C_2-C_{10} alkynyl, wherein a nonlimiting list of preferred substituent groups includes hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl and alkynyl.

In certain embodiments, conjugate linkers comprise 1-10 linker-nucleosides. In certain embodiments, conjugate linkers comprise 2-5 linker-nucleosides. In certain embodiments, conjugate linkers comprise exactly 3 linker-nucleosides. In certain embodiments, conjugate linkers comprise the TCA motif. In certain embodiments, such linker-nucleosides are modified nucleosides. In certain embodiments such linker-nucleosides comprise a modified sugar moiety. In certain embodiments, linker-nucleosides are unmodified. In certain embodiments, linker-nucleosides comprise an optionally protected heterocyclic base selected from a purine, substituted purine, pyrimidine or substituted pyrimidine. In certain embodiments, a cleavable moiety is a nucleoside selected from uracil, thymine, cytosine, 4-N-benzoylcytosine, 5-methyl cytosine, 4-N-benzoyl-5-methyl cytosine, adenine, 6-N-benzoyladenine, guanine and 2-N-isobutyrylguanine. It is typically desirable for linker-nucleosides to be cleaved from the oligomeric compound after it reaches a target tissue. Accordingly, linker-nucleosides are typically linked to one another and to the remainder of the oligomeric compound through cleavable bonds. In certain embodiments, such cleavable bonds are phosphodiester bonds.

Herein, linker-nucleosides are not considered to be part of the oligonucleotide. Accordingly, in embodiments in which an oligomeric compound comprises an oligonucleotide consisting of a specified number or range of linked nucleosides and/or a specified percent complementarity to a reference nucleic acid

and the oligomeric compound also comprises a conjugate group comprising a conjugate linker comprising linker-nucleosides, those linker-nucleosides are not counted toward the length of the oligonucleotide and are not used in determining the percent complementarity of the oligonucleotide for the reference nucleic acid. For example, an oligomeric compound may comprise (1) a modified oligonucleotide consisting of 8-30 nucleosides and (2) a conjugate group comprising 1-10 linker-nucleosides that are contiguous with the nucleosides of the modified oligonucleotide. The total number of contiguous linked nucleosides in such an oligomeric compound is more than 30. Alternatively, an oligomeric compound may comprise a modified oligonucleotide consisting of 8-30 nucleosides and no conjugate group. The total number of contiguous linked nucleosides in such an oligomeric compound is no more than 30. Unless otherwise indicated conjugate linkers comprise no more than 10 linker-nucleosides. In certain embodiments, conjugate linkers comprise no more than 5 linker-nucleosides. In certain embodiments, conjugate linkers comprise no more than 3 linker-nucleosides. In certain embodiments, conjugate linkers comprise no more than 2 linker-nucleosides. In certain embodiments, conjugate linkers comprise no more than 1 linker-nucleoside.

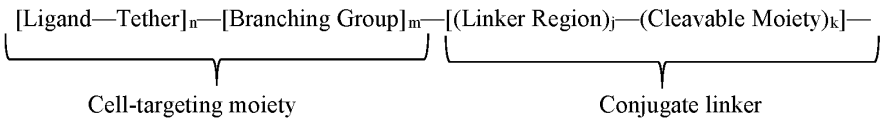
In certain embodiments, it is desirable for a conjugate group to be cleaved from the oligonucleotide. For example, in certain circumstances oligomeric compounds comprising a particular conjugate moiety are better taken up by a particular cell type, but once the oligomeric compound has been taken up, it is desirable that the conjugate group be cleaved to release the unconjugated or parent oligonucleotide. Thus, certain conjugate linkers may comprise one or more cleavable moieties. In certain embodiments, a cleavable moiety is a cleavable bond. In certain embodiments, a cleavable moiety is a group of atoms comprising at least one cleavable bond. In certain embodiments, a cleavable moiety comprises a group of atoms having one, two, three, four, or more than four cleavable bonds. In certain embodiments, a cleavable moiety is selectively cleaved inside a cell or subcellular compartment, such as a lysosome. In certain embodiments, a cleavable moiety is selectively cleaved by endogenous enzymes, such as nucleases.

In certain embodiments, a cleavable bond is selected from among: an amide, an ester, an ether, one or both esters of a phosphodiester, a phosphate ester, a carbamate, or a disulfide. In certain embodiments, a cleavable bond is one or both of the esters of a phosphodiester. In certain embodiments, a cleavable moiety comprises a phosphate or phosphodiester. In certain embodiments, the cleavable moiety is a phosphodiester linkage between an oligonucleotide and a conjugate moiety or conjugate group.

In certain embodiments, a cleavable moiety comprises or consists of one or more linker-nucleosides. In certain such embodiments, the one or more linker-nucleosides are linked to one another and/or to the remainder of the oligomeric compound through cleavable bonds. In certain embodiments, such cleavable bonds are unmodified phosphodiester bonds. In certain embodiments, a cleavable moiety is 2'-deoxy nucleoside that is attached to either the 3' or 5'-terminal nucleoside of an oligonucleotide by a phosphate internucleoside linkage and covalently attached to the remainder of the conjugate linker or conjugate moiety by a phosphate or phosphorothioate linkage. In certain such embodiments, the cleavable moiety is 2'-deoxyadenosine.

3. Certain cell-targeting conjugate moieties

In certain embodiments, a conjugate group comprises a cell-targeting conjugate moiety. In certain embodiments, a conjugate group has the general formula:



wherein n is from 1 to about 3, m is 0 when n is 1, m is 1 when n is 2 or greater, j is 1 or 0, and k is 1 or 0.

In certain embodiments, n is 1, j is 1 and k is 0. In certain embodiments, n is 1, j is 0 and k is 1. In certain embodiments, n is 1, j is 1 and k is 1. In certain embodiments, n is 2, j is 1 and k is 0. In certain embodiments, n is 2, j is 0 and k is 1. In certain embodiments, n is 2, j is 1 and k is 1. In certain embodiments, n is 3, j is 1 and k is 0. In certain embodiments, n is 3, j is 0 and k is 1. In certain embodiments, n is 3, j is 1 and k is 1.

In certain embodiments, conjugate groups comprise cell-targeting moieties that have at least one tethered ligand. In certain embodiments, cell-targeting moieties comprise two tethered ligands covalently attached to a branching group. In certain embodiments, cell-targeting moieties comprise three tethered ligands covalently attached to a branching group.

In certain embodiments, the cell-targeting moiety comprises a branching group comprising one or more groups selected from alkyl, amino, oxo, amide, disulfide, polyethylene glycol, ether, thioether and hydroxylamino groups. In certain embodiments, the branching group comprises a branched aliphatic group comprising groups selected from alkyl, amino, oxo, amide, disulfide, polyethylene glycol, ether, thioether and hydroxylamino groups. In certain such embodiments, the branched aliphatic group comprises groups selected from alkyl, amino, oxo, amide and ether groups. In certain such embodiments, the branched aliphatic group comprises groups selected from alkyl, amino and ether groups. In certain such embodiments, the branched aliphatic group comprises groups selected from alkyl and ether groups. In certain embodiments, the branching group comprises a mono or polycyclic ring system.

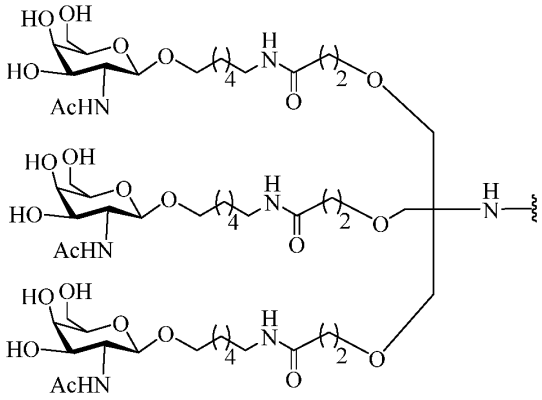
In certain embodiments, each tether of a cell-targeting moiety comprises one or more groups selected from alkyl, substituted alkyl, ether, thioether, disulfide, amino, oxo, amide, phosphodiester, and polyethylene glycol, in any combination. In certain embodiments, each tether is a linear aliphatic group comprising one or more groups selected from alkyl, ether, thioether, disulfide, amino, oxo, amide, and polyethylene glycol, in any combination. In certain embodiments, each tether is a linear aliphatic group comprising one or more groups selected from alkyl, phosphodiester, ether, amino, oxo, and amide, in any combination. In certain embodiments, each tether is a linear aliphatic group comprising one or more groups selected from alkyl, ether, amino, oxo, and amid, in any combination. In certain embodiments, each tether is a linear aliphatic group comprising one or more groups selected from alkyl, amino, and oxo, in any combination. In certain embodiments, each tether is a linear aliphatic group comprising one or more groups selected from alkyl and

oxo, in any combination. In certain embodiments, each tether is a linear aliphatic group comprising one or more groups selected from alkyl and phosphodiester, in any combination. In certain embodiments, each tether comprises at least one phosphorus linking group or neutral linking group. In certain embodiments, each tether comprises a chain from about 6 to about 20 atoms in length. In certain embodiments, each tether comprises a chain from about 10 to about 18 atoms in length. In certain embodiments, each tether comprises about 10 atoms in chain length.

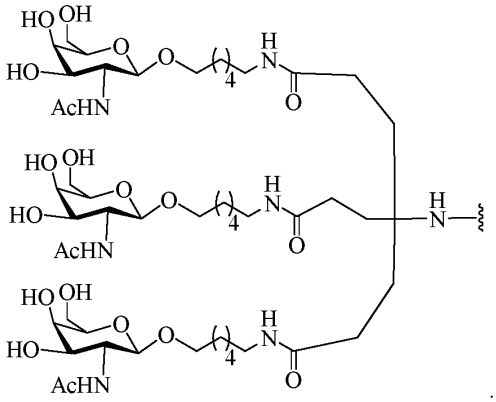
In certain embodiments, each ligand of a cell-targeting moiety has an affinity for at least one type of receptor on a target cell. In certain embodiments, each ligand has an affinity for at least one type of receptor on the surface of a mammalian liver cell. In certain embodiments, each ligand has an affinity for the hepatic asialoglycoprotein receptor (ASGP-R). In certain embodiments, each ligand is a carbohydrate. In certain embodiments, each ligand is, independently selected from galactose, N-acetyl galactosamine (GalNAc), mannose, glucose, glucosamine and fucose. In certain embodiments, each ligand is N-acetyl galactosamine (GalNAc). In certain embodiments, the cell-targeting moiety comprises 3 GalNAc ligands. In certain embodiments, the cell-targeting moiety comprises 2 GalNAc ligands. In certain embodiments, the cell-targeting moiety comprises 1 GalNAc ligand.

In certain embodiments, each ligand of a cell-targeting moiety is a carbohydrate, carbohydrate derivative, modified carbohydrate, polysaccharide, modified polysaccharide, or polysaccharide derivative. In certain such embodiments, the conjugate group comprises a carbohydrate cluster (*see*, *e.g.*, Maier et al., "Synthesis of Antisense Oligonucleotides Conjugated to a Multivalent Carbohydrate Cluster for Cellular Targeting," *Bioconjugate Chemistry*, 2003, 14, 18-29, or Rensen et al., "Design and Synthesis of Novel *N*-Acetylgalactosamine-Terminated Glycolipids for Targeting of Lipoproteins to the Hepatic Asiaglycoprotein Receptor," *J. Med. Chem.* 2004, 47, 5798-5808, which are incorporated herein by reference in their entirety). In certain such embodiments, each ligand is an amino sugar or a thio sugar. For example, amino sugars may be selected from any number of compounds known in the art, such as sialic acid, α-D-galactosamine, β-muramic acid, 2-deoxy-2-methylamino-L-glucopyranose, 4,6-dideoxy-4-formamido-2,3-di-*O*-methyl-D-mannopyranose, 2-deoxy-2-sulfoamino-D-glucopyranose and *N*-sulfo-D-glucosamine, and *N*-glycoloyl-α-neuraminic acid. For example, thio sugars may be selected from 5-Thio-β-D-glucopyranose, methyl 2,3,4-tri-*O*-acetyl-1-thio-6-*O*-trityl-α-D-glucopyranoside, 4-thio-β-D-galactopyranose, and ethyl 3,4,6,7-tetra-*O*-acetyl-2-deoxy-1,5-dithio-α-D-*gluco*-heptopyranoside.

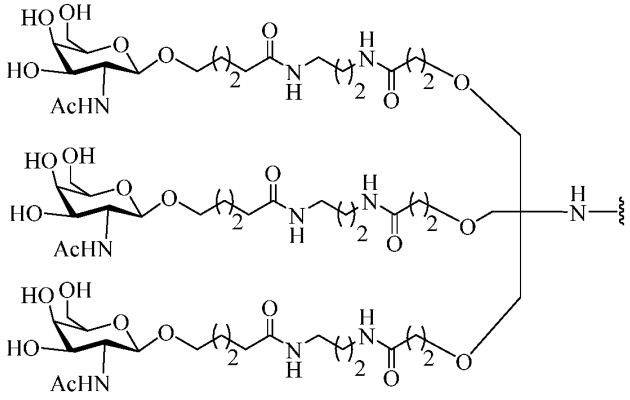
In certain embodiments, conjugate groups comprise a cell-targeting moiety having the formula:



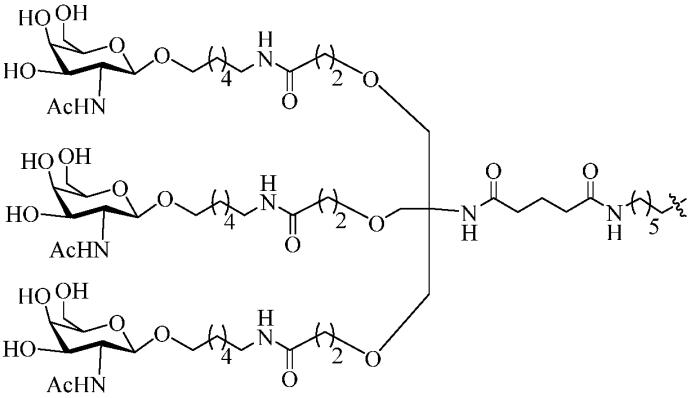
In certain embodiments, conjugate groups comprise a cell-targeting moiety having the formula:



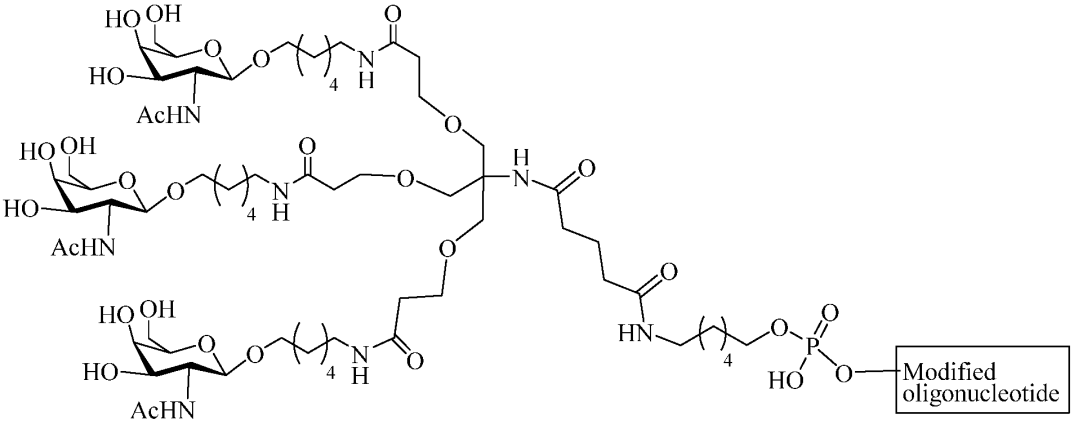
In certain embodiments, conjugate groups comprise a cell-targeting moiety having the formula:



In certain embodiments, compounds described herein comprise a conjugate group described herein as "THA-GalNAac$_3$". THA-GalNAc$_3$ is shown below without the optional cleavable moiety at the end of the linker region:



In certain embodiments, compounds described herein comprise THA-GalNAc$_3$-phosphate, also represented as (THA-GalNAc$_3$)o, having the formula:



wherein modified oligonucleotide represents a modified oligonucleotide.

Representative publications that teach the preparation of certain of the above noted conjugate groups and compounds comprising conjugate groups, tethers, conjugate linkers, branching groups, ligands, cleavable moieties as well as other modifications include without limitation, US 5,994,517, US 6,300,319, US 6,660,720, US 6,906,182, US 7,262,177, US 7,491,805, US 8,106,022, US 7,723,509, US 9,127,276, US 2006/0148740, US 2011/0123520, WO 2013/033230 and WO 2012/037254, Biessen et al., *J. Med. Chem.* 1995, 38, 1846-1852, Lee et al., *Bioorganic & Medicinal Chemistry* 2011,19, 2494-2500, Rensen et al., *J. Biol. Chem.* 2001, 276, 37577-37584, Rensen et al., *J. Med. Chem.* 2004, 47, 5798-5808, Sliedregt et al., *J.*

Med. Chem. 1999, 42, 609-618, and Valentijn et al., *Tetrahedron,* 1997, 53, 759-770, each of which is incorporated by reference herein in its entirety.

In certain embodiments, compounds described herein comprise modified oligonucleotides comprising a gapmer or fully modified motif and a conjugate group comprising at least one, two, or three GalNAc ligands. In certain embodiments compounds described herein comprise a conjugate group found in any of the following references: Lee, *Carbohydr Res*, 1978, 67, 509-514; Connolly et al., *J Biol Chem*, 1982, 257, 939-945; Pavia et al., *Int J Pep Protein Res*, 1983, 22, 539-548; Lee et al., *Biochem*, 1984, 23, 4255-4261; Lee et al., *Glycoconjugate J*, 1987, 4, 317-328; Toyokuni et al., *Tetrahedron Lett*, 1990, 31, 2673-2676; Biessen et al., *J Med Chem*, 1995, 38, 1538-1546; Valentijn et al., *Tetrahedron*, 1997, 53, 759-770; Kim et al., *Tetrahedron Lett*, 1997, 38, 3487-3490; Lee et al., *Bioconjug Chem*, 1997, 8, 762-765; Kato et al., *Glycobiol*, 2001, 11, 821-829; Rensen et al., *J Biol Chem*, 2001, 276, 37577-37584; Lee et al., *Methods Enzymol*, 2003, 362, 38-43; Westerlind et al., *Glycoconj J*, 2004, 21, 227-241; Lee et al., *Bioorg Med Chem Lett*, 2006, 16(19), 5132-5135; Maierhofer et al., *Bioorg Med Chem*, 2007, 15, 7661-7676; Khorev et al., *Bioorg Med Chem*, 2008, 16, 5216-5231; Lee et al., *Bioorg Med Chem*, 2011, 19, 2494-2500; Kornilova et al., Analyt Biochem, 2012, 425, 43-46; Pujol et al., *Angew Chemie Int Ed Engl*, 2012, 51, 7445-7448; Biessen et al., *J Med Chem*, 1995, 38, 1846-1852; Sliedregt et al., *J Med Chem*, 1999, 42, 609-618; Rensen et al., *J Med Chem*, 2004, 47, 5798-5808; Rensen et al., *Arterioscler Thromb Vasc Biol*, 2006, 26, 169-175; van Rossenberg et al., *Gene Ther*, 2004, 11, 457-464; Sato et al., *J Am Chem Soc*, 2004, 126, 14013-14022; Lee et al., *J Org Chem*, 2012, 77, 7564-7571; Biessen et al., *FASEB J*, 2000, 14, 1784-1792; Rajur et al., *Bioconjug Chem*, 1997, 8, 935-940; Duff et al., *Methods Enzymol*, 2000, 313, 297-321; Maier et al., *Bioconjug Chem*, 2003, 14, 18-29; Jayaprakash et al., *Org Lett*, 2010, 12, 5410-5413; Manoharan, *Antisense Nucleic Acid Drug Dev*, 2002, 12, 103-128; Merwin et al., *Bioconjug Chem*, 1994, 5, 612-620; Tomiya et al., Bioorg Med Chem, 2013, 21, 5275-5281; International applications WO1998/013381; WO2011/038356; WO1997/046098; WO2008/098788; WO2004/101619; WO2012/037254; WO2011/120053; WO2011/100131; WO2011/163121; WO2012/177947; WO2013/033230; WO2013/075035; WO2012/083185; WO2012/083046; WO2009/082607; WO2009/134487; WO2010/144740; WO2010/148013; WO1997/020563; WO2010/088537; WO2002/043771; WO2010/129709; WO2012/068187; WO2009/126933; WO2004/024757; WO2010/054406; WO2012/089352; WO2012/089602; WO2013/166121; WO2013/165816; U.S. Patents 4,751,219; 8,552,163; 6,908,903; 7,262,177; 5,994,517; 6,300,319; 8,106,022; 7,491,805; 7,491,805; 7,582,744; 8,137,695; 6,383,812; 6,525,031; 6,660,720; 7,723,509; 8,541,548; 8,344,125; 8,313,772; 8,349,308; 8,450,467; 8,501,930; 8,158,601; 7,262,177; 6,906,182; 6,620,916; 8,435,491; 8,404,862; 7,851,615; Published U.S. Patent Application Publications US2011/0097264; US2011/0097265; US2013/0004427; US2005/0164235; US2006/0148740; US2008/0281044; US2010/0240730; US2003/0119724; US2006/0183886; US2008/0206869; US2011/0269814; US2009/0286973; US2011/0207799; US2012/0136042; US2012/0165393; US2008/0281041; US2009/0203135; US2012/0035115; US2012/0095075;

US2012/0101148; US2012/0128760; US2012/0157509; US2012/0230938; US2013/0109817; US2013/0121954; US2013/0178512; US2013/0236968; US2011/0123520; US2003/0077829; US2008/0108801; and US2009/0203132; each of which is incorporated by reference in its entirety.

B. Certain Terminal Groups

In certain embodiments, oligomeric compounds comprise one or more terminal groups. In certain such embodiments, oligomeric compounds comprise a stabilized 5'-phophate. Stabilized 5'-phosphates include, but are not limited to 5'-phosphanates, including, but not limited to 5'-vinylphosphonates. In certain embodiments, terminal groups comprise one or more abasic nucleosides and/or inverted nucleosides. In certain embodiments, terminal groups comprise one or more 2'-linked nucleosides. In certain such embodiments, the 2'-linked nucleoside is an abasic nucleoside.

III. Oligomeric Duplexes

In certain embodiments, oligomeric compounds described herein comprise an oligonucleotide, having a nucleobase sequence complementary to that of a target nucleic acid. In certain embodiments, an oligomeric compound is paired with a second oligomeric compound to form an oligomeric duplex. Such oligomeric duplexes comprise a first oligomeric compound having a region complementary to a target nucleic acid and a second oligomeric compound having a region complementary to the first oligomeric compound. In certain embodiments, the first oligomeric compound of an oligomeric duplex comprises or consists of (1) a modified or unmodified oligonucleotide and optionally a conjugate group and (2) a second modified or unmodified oligonucleotide and optionally a conjugate group. Either or both oligomeric compounds of an oligomeric duplex may comprise a conjugate group. The oligonucleotides of each oligomeric compound of an oligomeric duplex may include non-complementary overhanging nucleosides.

IV. Antisense Activity

In certain embodiments, oligomeric compounds and oligomeric duplexes are capable of hybridizing to a target nucleic acid, resulting in at least one antisense activity; such oligomeric compounds and oligomeric duplexes are antisense compounds. In certain embodiments, antisense compounds have antisense activity when they reduce or inhibit the amount or activity of a target nucleic acid by 25% or more in the standard cell assay. In certain embodiments, antisense compounds selectively affect one or more target nucleic acid. Such antisense compounds comprise a nucleobase sequence that hybridizes to one or more target nucleic acid, resulting in one or more desired antisense activity and does not hybridize to one or more non-target nucleic acid or does not hybridize to one or more non-target nucleic acid in such a way that results in significant undesired antisense activity.

In certain antisense activities, hybridization of an antisense compound to a target nucleic acid results in recruitment of a protein that cleaves the target nucleic acid. For example, certain antisense compounds result in RNase H mediated cleavage of the target nucleic acid. RNase H is a cellular endonuclease that cleaves the RNA strand of an RNA:DNA duplex. The DNA in such an RNA:DNA duplex need not be unmodified DNA. In certain embodiments, antisense compounds described herein are sufficiently "DNA-

like" to elicit RNase H activity. In certain embodiments, one or more non-DNA-like nucleoside in the gap of a gapmer is tolerated.

In certain antisense activities, an antisense compound or a portion of an antisense compound is loaded into an RNA-induced silencing complex (RISC), ultimately resulting in cleavage of the target nucleic acid. For example, certain antisense compounds result in cleavage of the target nucleic acid by Argonaute. Antisense compounds that are loaded into RISC are RNAi compounds. RNAi compounds may be double-stranded (siRNA) or single-stranded (ssRNA).

In certain embodiments, hybridization of an antisense compound to a target nucleic acid does not result in recruitment of a protein that cleaves that target nucleic acid. In certain embodiments, hybridization of the antisense compound to the target nucleic acid results in alteration of splicing of the target nucleic acid. In certain embodiments, hybridization of an antisense compound to a target nucleic acid results in inhibition of a binding interaction between the target nucleic acid and a protein or other nucleic acid. In certain embodiments, hybridization of an antisense compound to a target nucleic acid results in alteration of translation of the target nucleic acid.

Antisense activities may be observed directly or indirectly. In certain embodiments, observation or detection of an antisense activity involves observation or detection of a change in an amount of a target nucleic acid or protein encoded by such target nucleic acid, a change in the ratio of splice variants of a nucleic acid or protein and/or a phenotypic change in a cell or animal.

V. Certain Target Nucleic Acids

In certain embodiments, oligomeric compounds comprise or consist of an oligonucleotide comprising a region that is complementary to a target nucleic acid. In certain embodiments, the target nucleic acid is an endogenous RNA molecule. In certain embodiments, the target nucleic acid encodes a protein. In certain such embodiments, the target nucleic acid is selected from: a mature mRNA and a pre-mRNA, including intronic, exonic and untranslated regions. In certain embodiments, the target RNA is a mature mRNA. In certain embodiments, the target nucleic acid is a pre-mRNA. In certain such embodiments, the target region is entirely within an intron. In certain embodiments, the target region spans an intron/exon junction. In certain embodiments, the target region is at least 50% within an intron. In certain embodiments, the target nucleic acid is the RNA transcriptional product of a retrogene. In certain embodiments, the target nucleic acid is a non-coding RNA. In certain such embodiments, the target non-coding RNA is selected from: a long non-coding RNA, a short non-coding RNA, an intronic RNA molecule.

A. Complementarity/Mismatches to the Target Nucleic Acid

It is possible to introduce mismatch bases without eliminating activity. For example, Gautschi et al (*J. Natl. Cancer Inst.* 93:463-471, March 2001) demonstrated the ability of an oligonucleotide having 100% complementarity to the bcl-2 mRNA and having 3 mismatches to the bcl-xL mRNA to reduce the expression of both bcl-2 and bcl-xL in vitro and in vivo. Furthermore, this oligonucleotide demonstrated potent anti-tumor activity in vivo. Maher and Dolnick (Nuc. Acid. Res. 16:3341-3358, 1988) tested a series of tandem

14 nucleobase oligonucleotides, and a 28 and 42 nucleobase oligonucleotides comprised of the sequence of two or three of the tandem oligonucleotides, respectively, for their ability to arrest translation of human DHFR in a rabbit reticulocyte assay. Each of the three 14 nucleobase oligonucleotides alone was able to inhibit translation, albeit at a more modest level than the 28 or 42 nucleobase oligonucleotides.

In certain embodiments, oligonucleotides are complementary to the target nucleic acid over the entire length of the oligonucleotide. In certain embodiments, oligonucleotides are 99%, 95%, 90%, 85%, or 80% complementary to the target nucleic acid. In certain embodiments, oligonucleotides are at least 80% complementary to the target nucleic acid over the entire length of the oligonucleotide and comprise a region that is 100% or fully complementary to a target nucleic acid. In certain embodiments, the region of full complementarity is from 6 to 20, 10 to 18, or 18 to 20 nucleobases in length.

In certain embodiments, oligonucleotides comprise one or more mismatched nucleobases relative to the target nucleic acid. In certain embodiments, antisense activity against the target is reduced by such mismatch, but activity against a non-target is reduced by a greater amount. Thus, in certain embodiments selectivity of the oligonucleotide is improved. In certain embodiments, the mismatch is specifically positioned within an oligonucleotide having a gapmer motif. In certain embodiments, the mismatch is at position 1, 2, 3, 4, 5, 6, 7, or 8 from the 5'-end of the gap region. In certain embodiments, the mismatch is at position 9, 8, 7, 6, 5, 4, 3, 2, 1 from the 3'-end of the gap region. In certain embodiments, the mismatch is at position 1, 2, 3, or 4 from the 5'-end of the wing region. In certain embodiments, the mismatch is at position 4, 3, 2, or 1 from the 3'-end of the wing region.

B. FXI

In certain embodiments, oligomeric compounds comprise or consist of an oligonucleotide comprising a region that is complementary to a target nucleic acid, wherein the target nucleic acid is FXI. In certain embodiments, FXI nucleic acid has the sequence set forth in SEQ ID NO: 1 (the complement of GENBANK Accession No: NT_022792.17 truncated from nucleobase 19598000 to 19624000) and SEQ ID NO: 2 (GENBANK Accession No: NM_000128.3).

In certain embodiments, methods comprise contacting a cell with an oligomeric compound disclosed herein. In certain embodiments, methods comprise administering an oligomeric compound disclosed herein to an animal, thereby contacting a cell in the animal. In certain embodiments, contacting a cell with an oligomeric compound comprising a modified oligonucleotide complementary to SEQ ID NO: 1 or SEQ ID NO: 2 reduces the amount of FXI RNA, and in certain embodiments reduces the amount of FXI protein. In certain embodiments, the oligomeric compound consists of a conjugate group attached to the 5' end of a modified oligonucleotide. In certain embodiments, contacting a cell in an animal with an oligomeric compound comprising a modified oligonucleotide complementary to SEQ ID NO: 1 or SEQ ID NO: 2 treats, prevents, or ameliorates a thromboembolic condition. In certain embodiments, the thromboembolic condition is deep vein thrombosis, venous or arterial thrombosis, pulmonary embolism, myocardial infarction, stroke, thrombosis associated with chronic kidney disease or end-stage renal disease (ESRD), including thrombosis

associated with dialysis, or other procoagulant condition. In certain embodiments, the oligomeric compound consists of a conjugate group attached to the 5' end of a modified oligonucleotide. In certain embodiments, contacting a cell in an animal with an oligomeric compound comprising a modified oligonucleotide complementary to SEQ ID NO: 1 or SEQ ID NO: 2 treats, prevents, or ameliorates a thromboembolic condition without increasing bleeding risk. In certain embodiments, the thromboembolic condition is deep vein thrombosis, venous or arterial thrombosis, pulmonary embolism, myocardial infarction, stroke, thrombosis associated with chronic kidney disease or end-stage renal disease (ESRD), including thrombosis associated with dialysis, or other procoagulant condition. In certain embodiments, the oligomeric compound consists of a conjugate group attached to the 5' end of a modified oligonucleotide.

A FXI RNA may be quantified, *e.g.*, by quantitative PCR. FXI proteins may be quantified with standard protein quantification tests, *e.g.*, ELISA. The FXI protein may be an inactive form (zymogen). The FXI protein may be an active form (FXIa). The active form of FXI may promote converting FIX from its inactive form (FIX) to its active form (FIXa). FXI activity may be assessed with a blood test that characterizes coagulation of blood. Non-limiting examples of such blood tests are a partial thromboplastin time (PTT) test or activated partial thromboplastin time test (aPTT or APTT). FXI activity in a test plasma sample may be assayed by adding the test plasma sample to a plasma sample that is immunodepleted of FXI and comparing clotting of the resulting combined sample to a reference sample with a reference amount of FXI.

In certain embodiments, contacting a cell in an animal with an oligomeric compound comprising a modified oligonucleotide complementary to SEQ ID NO: 1 or SEQ ID NO: 2 treats, prevents, or ameliorates a thromboembolic condition. In certain embodiments, the thromboembolic condition is deep vein thrombosis, venous or arterial thrombosis, pulmonary embolism, myocardial infarction, stroke, thrombosis associated with chronic kidney disease or end-stage renal disease (ESRD), including thrombosis associated with dialysis, or other procoagulant condition. In certain embodiments, the oligomeric compound consists of a conjugate group attached to the 5' end of a modified oligonucleotide. In certain embodiments, contacting a cell in an animal with an oligomeric compound comprising a modified oligonucleotide complementary to SEQ ID NO: 1 or SEQ ID NO: 2 treats, prevents, or ameliorates a thromboembolic condition without increasing bleeding risk. In certain embodiments, the thromboembolic condition is deep vein thrombosis, venous or arterial thrombosis, pulmonary embolism, myocardial infarction, stroke, thrombosis associated with chronic kidney disease or end-stage renal disease (ESRD), including thrombosis associated with dialysis, or other procoagulant condition. In certain embodiments, the oligomeric compound consists or consists essentially of a conjugate group attached to the 5' end of a modified oligonucleotide.

C. Certain Target Nucleic Acids in Certain Tissues

In certain embodiments, oligomeric compounds comprise or consist of an oligonucleotide comprising a region that is complementary to a target nucleic acid, wherein the target nucleic acid is expressed in a pharmacologically relevant tissue. In certain embodiments, the pharmacologically relevant tissues are the

cells and tissues that comprise the alimentary and/or excretory system. Such cells and tissues include the liver, kidney, and pancreas.

VI. Certain Pharmaceutical Compositions

In certain embodiments, pharmaceutical compositions described herein comprise one or more oligomeric compounds. In certain embodiments, the one or more oligomeric compounds each comprise a modified oligonucleotide. In certain embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable diluent or carrier. In certain embodiments, a pharmaceutical composition comprises a sterile saline solution and one or more oligomeric compounds. In certain embodiments, a pharmaceutical composition consists or consists essentially of a sterile saline solution and one or more oligomeric compounds. In certain embodiments, the sterile saline is pharmaceutical grade saline. In certain embodiments, a pharmaceutical composition comprises one or more oligomeric compounds and sterile water. In certain embodiments, a pharmaceutical composition consists or consists essentially of one or more oligomeric compounds and sterile water. In certain embodiments, the sterile water is pharmaceutical grade water. In certain embodiments, the pharmaceutically acceptable diluent or carrier is distilled water for injection. In certain embodiments, a pharmaceutical composition comprises one or more oligomeric compound and phosphate-buffered saline (PBS). In certain embodiments, a pharmaceutical composition consists or consists essentially of one or more oligomeric compounds and PBS. In certain embodiments, the sterile PBS is pharmaceutical grade PBS. In certain embodiments, a pharmaceutical composition comprises one or more oligomeric compound and artificial cerebrospinal fluid. In certain embodiments, the sterile PBS is pharmaceutical grade PBS. In certain embodiments, a pharmaceutical composition consists or consists essentially of artificial cerebrospinal fluid. In certain embodiments, the artificial cerebrospinal fluid is pharmaceutical grade.

In certain embodiments, pharmaceutical compositions comprise one or more oligomeric compounds disclosed herein and one or more excipients. In certain embodiments, excipients are selected from water, salt solutions, alcohol, polyethylene glycols, gelatin, lactose, amylase, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose and polyvinylpyrrolidone.

In certain embodiments, oligomeric compounds may be admixed with pharmaceutically acceptable active and/or inert substances for the preparation of pharmaceutical compositions or formulations. Compositions and methods for the formulation of pharmaceutical compositions depend on a number of criteria, including, but not limited to, route of administration, extent of disease, or dose to be administered.

In certain embodiments, pharmaceutical compositions comprising an oligomeric compound disclosed herein encompass any pharmaceutically acceptable salts of the oligomeric compound, esters of the oligomeric compound, or salts of such esters. In certain embodiments, pharmaceutical compositions comprising oligomeric compounds comprising one or more oligonucleotide, upon administration to an animal, including a human, are capable of providing (directly or indirectly) the biologically active metabolite or residue thereof.

Accordingly, for example, the disclosure is also drawn to pharmaceutically acceptable salts of oligomeric compounds, prodrugs, pharmaceutically acceptable salts of such prodrugs, and other bioequivalents. Suitable pharmaceutically acceptable salts include, but are not limited to, sodium and potassium salts. In certain embodiments, prodrugs comprise one or more conjugate group attached to an oligonucleotide, wherein the conjugate group is cleaved by endogenous nucleases within the body.

Lipid moieties have been used in nucleic acid therapies in a variety of methods. In certain such methods, the nucleic acid, such as an oligomeric compound, is introduced into preformed liposomes or lipoplexes made of mixtures of cationic lipids and neutral lipids. In certain methods, DNA complexes with mono- or poly-cationic lipids are formed without the presence of a neutral lipid. In certain embodiments, a lipid moiety is selected to increase distribution of a pharmaceutical agent to a particular cell or tissue. In certain embodiments, a lipid moiety is selected to increase distribution of a pharmaceutical agent to fat tissue. In certain embodiments, a lipid moiety is selected to increase distribution of a pharmaceutical agent to muscle tissue.

In certain embodiments, pharmaceutical compositions disclosed herein comprise a delivery system. Examples of delivery systems include, but are not limited to, liposomes and emulsions. Certain delivery systems are useful for preparing certain pharmaceutical compositions including those comprising hydrophobic compounds. In certain embodiments, certain organic solvents such as dimethylsulfoxide are used.

In certain embodiments, pharmaceutical compositions comprise one or more tissue-specific delivery molecules designed to deliver oligomeric compounds described herein to specific tissues or cell types. For example, in certain embodiments, pharmaceutical compositions include liposomes coated with a tissue-specific antibody.

In certain embodiments, pharmaceutical compositions comprise a co-solvent system. Certain of such co-solvent systems comprise, for example, benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. In certain embodiments, such co-solvent systems are used for hydrophobic compounds. A non-limiting example of such a co-solvent system is the VPD co-solvent system, which is a solution of absolute ethanol comprising 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant Polysorbate 80™ and 65% w/v polyethylene glycol 300. The proportions of such co-solvent systems may be varied considerably without significantly altering their solubility and toxicity characteristics. Furthermore, the identity of co-solvent components may be varied: for example, other surfactants may be used instead of Polysorbate 80™; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, *e.g.*, polyvinyl pyrrolidone; and other sugars or polysaccharides may substitute for dextrose.

In certain embodiments, pharmaceutical compositions disclosed herein are prepared for oral administration. In certain embodiments, pharmaceutical compositions are prepared for buccal administration. In certain embodiments, a pharmaceutical composition is prepared for administration by injection (*e.g.*,

intravenous, subcutaneous, intramuscular, intrathecal (IT), intracerebroventricular (ICV), etc.). In certain of such embodiments, a pharmaceutical composition comprises a carrier and is formulated in aqueous solution, such as water or physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. In certain embodiments, other ingredients are included (*e.g.*, ingredients that aid in solubility or serve as preservatives). In certain embodiments, injectable suspensions are prepared using appropriate liquid carriers, suspending agents and the like. Certain pharmaceutical compositions for injection are presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers. Certain pharmaceutical compositions for injection are suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Certain solvents suitable for use in pharmaceutical compositions for injection include, but are not limited to, lipophilic solvents and fatty oils, such as sesame oil, synthetic fatty acid esters, such as ethyl oleate or triglycerides, and liposomes. Aqueous injection suspensions may contain.

Under certain conditions, certain compounds disclosed herein act as acids. Although such compounds may be drawn or described in protonated (free acid) form, in ionized (anion) form, or ionized and in association with a cation (salt) form, aqueous solutions of such compounds exist in equilibrium among such forms. For example, a phosphate linkage of an oligonucleotide in aqueous solution exists in equilibrium among free acid, anion, and salt forms. Unless otherwise indicated, compounds described herein are intended to include all such forms. Moreover, certain oligonucleotides have several such linkages, each of which is in equilibrium. Thus, oligonucleotides in solution exist in an ensemble of forms at multiple positions all at equilibrium. The term "oligonucleotide" is intended to include all such forms. Drawn structures necessarily depict a single form. Nevertheless, unless otherwise indicated, such drawings are likewise intended to include corresponding forms. Herein, a structure depicting the free acid of a compound followed by the term "or salts thereof" expressly includes all such forms that may be fully or partially protonated/de-protonated/in association with a cation. In certain instances, one or more specific cation is identified.

In certain embodiments, oligomeric compounds disclosed herein are in aqueous solution with sodium. In certain embodiments, oligomeric compounds are in aqueous solution with potassium. In certain embodiments, oligomeric compounds are in PBS. In certain embodiments, oligomeric compounds are in water. In certain such embodiments, the pH of the solution is adjusted with NaOH and/or HCl to achieve a desired pH.

Herein, certain specific doses are described. A dose may be in the form of a dosage unit. For clarity, a dose (or dosage unit) of an oligomeric compound in milligrams indicates the mass of the free acid form of the oligomeric compound. As described above, in aqueous solution, the free acid is in equilibrium with anionic and salt forms. However, for the purpose of calculating dose, it is assumed that the oligomeric compound exists as a solvent-free, sodium-acetate free, anhydrous, conjugated free acid. For example, where an oligomeric compound is in solution comprising sodium (*e.g.*, saline), the oligomeric compound may be partially or fully de-protonated and in association with Na^+ ions. However, the mass of the protons are

nevertheless counted toward the weight of the dose, and the mass of the Na^+ ions are not counted toward the weight of the dose. Thus, for example, a dose, or dosage unit, of 80 mg of Compound No. 957943 equals the number of fully protonated molecules that weighs 80 mg. This would be equivalent to 84 mg of solvent-free, sodium-acetate free, anhydrous sodiated Compound No. 957943. When an oligomeric compound comprises a conjugate, the mass of conjugate is included in calculating the dose of such oligomeric compound.

VII. Certain Dosage Amounts

In certain embodiments, pharmaceutical compositions described herein are administered in the form of a dosage unit. The dosage unit may be prepared for injection. The dosage unit may be prepared for infusion. In certain embodiments, the dosage unit comprises an oligomeric compound disclosed herein and a pharmaceutically acceptable carrier or diluent. In certain embodiments, the dosage unit consists or consists essentially of an oligomeric compound disclosed herein and a pharmaceutically acceptable carrier or diluent. In certain embodiments, the oligomeric compound comprises a modified oligonucleotide having the nucleobase sequence of SEQ ID NO: 3. In certain embodiments, the oligomeric compound is Compound No. 957943.

In certain embodiments, the oligomeric compound is present in the dosage unit at an amount selected from 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 105 mg, 110 mg, 115 mg, 120 mg, 125 mg, 130 mg, 135 mg, 140 mg, 145 mg, 150 mg, 155 mg, 160 mg, 165 mg, 170 mg, 175 mg, 180 mg, 185 mg, 190 mg, 195 mg, 200 mg, 205 mg, 210 mg, 215 mg, 220 mg, 225 mg, 230 mg, 235 mg, 240 mg, 245 mg, 250 mg, 255 mg, 260 mg, 265 mg, 270 mg, 275 mg, 280 mg, 285 mg, 290 mg, 295 mg, and 300 mg. In certain embodiments, the oligomeric compound is present in the dosage unit at an amount selected from about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, and about 300 mg.

In certain embodiments, the oligomeric compound is present in the dosage unit at an amount selected from 20 mg, 21 mg, 22 mg, 23 mg, 24 mg, 25 mg, 26 mg, 27 mg, 28 mg, 29 mg, 30 mg, 31 mg, 32 mg, 33 mg, 34 mg, 35 mg, 36 mg, 37 mg, 38 mg, 39 mg, 40 mg, 41 mg, 42 mg, 43 mg, 44 mg, 45 mg, 46 mg, 47 mg, 48 mg, 49 mg, 50 mg, 51 mg, 52 mg, 53 mg, 54 mg, 55 mg, 56 mg, 57 mg, 58 mg, 59 mg, 60 mg, 61 mg, 62 mg, 63 mg, 64 mg, 65 mg, 66 mg, 67 mg, 68 mg, 69 mg, 70 mg, 71 mg, 72 mg, 73 mg, 74 mg, 75 mg, 76 mg, 77 mg, 78 mg, 79 mg, 80 mg, 81 mg, 82 mg, 83 mg, 84 mg, 85 mg, 86 mg, 87 mg, 88 mg, 89 mg, 90 mg, 91

mg, 92 mg, 93 mg, 94 mg, 95 mg, 96 mg, 97 mg, 98 mg, 99 mg, 100 mg, 101 mg, 102 mg, 103 mg, 104 mg, 105 mg, 106 mg, 107 mg, 108 mg, 109 mg, 110 mg, 111 mg, 112 mg, 113 mg, 114 mg, 115 mg, 116 mg, 117 mg, 118 mg, 119 mg, 120 mg, 121 mg, 122 mg, 123 mg, 124 mg, 125 mg, 126 mg, 127 mg, 128 mg, 129 mg, 130 mg, 131 mg, 132 mg, 133 mg, 134 mg, 135 mg, 136 mg, 137 mg, 138 mg, 139 mg, and 140 mg. In certain embodiments, the oligomeric compound is present in the dosage unit at an amount selected from about 20 mg, about 21 mg, about 22 mg, about 23 mg, about 24 mg, about 25 mg, about 26 mg, about 27 mg, about 28 mg, about 29 mg, about 30 mg, about 31 mg, about 32 mg, about 33 mg, about 34 mg, about 35 mg, about 36 mg, about 37 mg, about 38 mg, about 39 mg, about 40 mg, about 41 mg, about 42 mg, about 43 mg, about 44 mg, about 45 mg, about 46 mg, about 47 mg, about 48 mg, about 49 mg, about 50 mg, about 51 mg, about 52 mg, about 53 mg, about 54 mg, about 55 mg, about 56 mg, about 57 mg, about 58 mg, about 59 mg, about 60 mg, about 61 mg, about 62 mg, about 63 mg, about 64 mg, about 65 mg, about 66 mg, about 67 mg, about 68 mg, about 69 mg, about 70 mg, about 71 mg, about 72 mg, about 73 mg, about 74 mg, about 75 mg, about 76 mg, about 77 mg, about 78 mg, about 79 mg, about 80 mg, about 81 mg, about 82 mg, about 83 mg, about 84 mg, about 85 mg, about 86 mg, about 87 mg, about 88 mg, about 89 mg, about 90 mg, about 91 mg, about 92 mg, about 93 mg, about 94 mg, about 95 mg, about 96 mg, about 97 mg, about 98 mg, about 99 mg, about 100 mg, about 101 mg, about 102 mg, about 103 mg, about 104 mg, about 105 mg, about 106 mg, about 107 mg, about 108 mg, about 109 mg, about 110 mg, about 111 mg, about 112 mg, about 113 mg, about 114 mg, about 115 mg, about 116 mg, about 117 mg, about 118 mg, about 119 mg, about 120 mg, about 121 mg, about 122 mg, about 123 mg, about 124 mg, about 125 mg, about 126 mg, about 127 mg, about 128 mg, about 129 mg, about 130 mg, about 131 mg, about 132 mg, about 133 mg, about 134 mg, about 135 mg, about 136 mg, about 137 mg, about 138 mg, about 139 mg, and about 140 mg.

In certain embodiments, the oligomeric compound is present in the dosage unit at an amount selected from 75.0 mg, 75.1 mg, 75.2 mg, 75.3 mg, 75.4 mg, 75.5 mg, 75.6 mg, 75.7 mg, 75.8 mg, 75.9 mg, 76.0 mg, 76.1 mg, 76.2 mg, 76.3 mg. 76.4 mg, 76.5 mg, 76.6 mg, 76.7 mg, 76.8 mg, 76.9 mg, 77.0 mg, 77.1 mg, 77.2 mg, 77.3 mg, 77.4 mg, 77.5 mg, 77.6 mg, 77.7 mg, 77.8 mg, 77.9 mg, 78.0 mg, 78.1 mg, 78.2 mg, 78.3 mg. 78.4 mg, 78.5 mg, 78.6 mg, 78.7 mg, 78.8 mg, 78.9 mg, 79.0 mg, 79.1 mg, 79.2 mg, 79.3 mg, 79.4 mg, 79.5 mg, 79.6 mg, 79.7 mg, 79.8 mg, 79.9 mg, 80.0 mg, 80.1 mg, 80.2 mg, 80.3 mg. 80.4 mg, 80.5 mg, 80.6 mg, 80.7 mg, 80.8 mg, 80.9 mg, 81.0 mg, 81.1 mg, 81.2 mg, 81.3 mg, 81.4 mg, 81.5 mg, 81.6 mg, 81.7 mg, 81.8 mg, 81.9 mg, 82.0 mg, 82.1 mg, 82.2 mg, 82.3 mg. 82.4 mg, 82.5 mg, 82.6 mg, 82.7 mg, 82.8 mg, 82.9 mg, 83.0 mg, 83.1 mg, 83.2 mg, 83.3 mg, 83.4 mg, 83.5 mg, 83.6 mg, 83.7 mg, 83.8 mg, 83.9 mg, 84.0 mg, 84.1 mg, 84.2 mg, 84.3 mg. 84.4 mg, 84.5 mg, 84.6 mg, 84.7 mg, 84.8 mg, 84.9 mg, and 85.0 mg. In certain embodiments, the oligomeric compound is present in the dosage unit at an amount selected from about 75.0 mg, about 75.1 mg, about 75.2 mg, about 75.3 mg, about 75.4 mg, about 75.5 mg, about 75.6 mg, about 75.7 mg, about 75.8 mg, about 75.9 mg, about 76.0 mg, about 76.1 mg, about 76.2 mg, about 76.3 mg. about about 76.4 mg, about 76.5 mg, about 76.6 mg, about 76.6 about 76.7 mg, about 76.8 mg, about 76.9 mg, about 77.0 mg, about 77.1 mg, about 77.2 mg, about 77.3 mg, about 77.4 mg, about 77.5 mg, about 77.6 mg, about 77.7

mg, about 77.8 mg, about 77.9 mg, about 78.0 mg, about 78.1 mg, about 78.2 mg, about 78.3 mg. about 78.4 mg, about 78.5 mg, about 78.6 mg, about 78.7 mg, about 78.8 mg, about 78.9 mg, about 79.0 mg, about 79.1 mg, about 79.2 mg, about 79.3 mg, about 79.4 mg, about 79.5 mg, about 79.6 mg, about 79.7 mg, about 79.8 mg, about 79.9 mg, about 80.0 mg, about 80.1 mg, about 80.2 mg, about 80.3 mg. about 80.4 mg, about 80.5 mg, about 80.6 mg, about 80.7 mg, about 80.8 mg, about 80.9 mg, about 81.0 mg, about 81.1 mg, about 81.2 mg, about 81.3 mg, about 81.4 mg, about 81.5 mg, about 81.6 mg, about 81.7 mg, about 81.8 mg, about 81.9 mg, about 82.0 mg, about 82.1 mg, about 82.2 mg, about 82.3 mg. about 82.4 mg, about 82.5 mg, about 82.6 mg, about 82.7 mg, about 82.8 mg, about 82.9 mg, about 83.0 mg, about 83.1 mg, about 83.2 mg, about 83.3 mg, about 83.4 mg, about 83.5 mg, about 83.6 mg, about 83.7 mg, about 83.8 mg, about 83.9 mg, about 84.0 mg, about 84.1 mg, about 84.2 mg, about 84.3 mg. about 84.4 mg, about 84.5 mg, about 84.6 mg, about 84.7 mg, about 84.8 mg, about 84.9 mg, and about 85.0 mg.

In certain embodiments, the oligomeric compound is present in the dosage unit at an amount that falls within a range. In certain embodiments, the range is selected from 10 mg to 140 mg, from 10 mg to 130 mg, from 10 mg to 120 mg, from 10 mg to 110 mg, from 10 mg to 100 mg, from 10 mg to 90 mg, from 10 mg to 80 mg, from 10 mg to 70 mg, from 10 mg to 60 mg, from 10 mg to 50 mg, from 10 mg to 40 mg, from 10 mg to 30 mg, from 10 mg to 20 mg, from 20 mg to 140 mg, from 20 mg to 130 mg, from 20 mg to 120 mg, from 20 mg to 110 mg, from 20 mg to 100 mg, from 20 mg to 90 mg, from 20 mg to 80 mg, from 20 mg to 70 mg, from 20 mg to 60 mg, from 20 mg to 50 mg, from 20 mg to 40 mg, from 20 mg to 30 mg, from 30 mg to 140 mg, from 30 mg to 130 mg, from 30 mg to 120 mg, from 30 mg to 110 mg, from 30 mg to 100 mg, from 30 mg to 90 mg, from 30 mg to 80mg, from 30 mg to 70 mg, from 30 mg to 60 mg, from 30 mg to 50 mg, from 30 mg to 40mg, from 40 mg to 140 mg, from 40 mg to 130 mg, from 40 mg to 120 mg, from from 40 mg to 110 mg, from 40 mg to 100 mg, from 40 mg to 90 mg, from 40 mg to 80 mg, from 40 mg to 70 mg, from 40 mg to 60 mg, from 40 mg to 50 mg, from 50 mg to 140 mg, from 50 mg to 130 mg, from 50 mg to 120 mg, from 50 mg to 110 mg, from 50 mg to 100 mg, from 50 mg to 90 mg, from 50 mg to 80 mg, from 50 mg to 70 mg, from 50 mg to 60 mg, from 60 mg to 140 mg, from 60 mg to 130 mg, from 60 mg to 120 mg, from 60 mg to 110 mg, from 60 mg to 100 mg, from 60 mg to 90 mg, from 60 mg to 80 mg, from 60 mg to 70 mg, from 70 mg to 140 mg, from 70 mg to 130 mg, from 70 mg to 120 mg, from 70 mg to 110 mg, from 70 mg to 100 mg, from 70 mg to 90 mg, from 70 mg to 80 mg, from 80 mg to 140 mg, from 80 mg to 130 mg, from 80 mg to 120 mg, from 80 mg to 110 mg, from 80 mg to 100 mg, from 80 mg to 90 mg, from 90 mg to 140 mg, from 90 mg to 130 mg, from 90 mg to 120 mg, from 90 mg to 110mg, from 90 mg to 100 mg, from 100 mg to 140 mg, from 100 mg to 130 mg, from 100 mg to 120 mg, from 100 mg to 110 mg, from 110 mg to 140 mg, from 110 mg to 130 mg, from 110 mg to 120 mg, from 120 mg to 140 mg, from 120 mg to 130 mg, from 130 mg to 140 mg, from 65 mg to 95 mg, from 65 mg to 90 mg, from 65 mg to 85 mg from 65 mg to 80 mg, from 65 mg to 75 mg, from 65 mg to 70 mg, from 70 mg to 95 mg, from 70 mg to 85 mg, from 70 mg to 75 mg, from 75 mg to 100 mg, from 75 mg to 95 mg, from 75 mg to 90 mg, from 75 mg to 85 mg, from 75 mg to 80 mg, from 80 mg to 95 mg, from 80 mg to 85 mg, from 85 mg to 100 mg, from 85 mg to 90 mg, from 90

mg to 95 mg, from 95 mg to 100 mg, from 80 mg to 89 mg, from 80 mg to 88 mg, from 80 mg to 87 mg, from 80 mg to 86 mg, from 80 mg to 84 mg, from 80 mg to 83 mg, from 80 mg to 82 mg, from 80 mg to 81 mg, from 81 mg to 90 mg, from 82 mg to 89 mg, from 82 mg to 88 mg, from 82 mg to 87 mg, from 82 mg to 86 mg, from 82 mg to 85 mg, from 82 mg to 84 mg, from 82 mg to 83 mg, from 83 mg to 90 mg, from 83 mg to 89 mg, from 83 mg to 88 mg, from 83 mg to 87 mg, from 83 mg to 86 mg, from 83 mg to 85 mg, from 83 mg to 84 mg, from 84 mg to 90 mg, from 84 mg to 89 mg, from 84 mg to 88 mg, from 84 mg to 87 mg, from 84 mg to 86 mg, from 84 mg to 85 mg, from 85 mg to 89 mg, from 85 mg to 88 mg, from 85 mg to 87 mg, from 85 mg to 86 mg, from 86 mg to 90 mg, from 86 mg to 89 mg, from 86 mg to 88 mg, from 86 mg to 87 mg, from 87 mg to 90 mg, from 87 mg to 89 mg, from 87 mg to 88 mg, from 88 mg to 90 mg, from 88 mg to 89 mg, and from 89 mg to 90 mg.

In certain embodiments, the oligomeric compound is present in the dosage unit at an amount that is less than about 300 mg, less than about 295 mg, less than about 290 mg, less than about 285 mg, less than about 280 mg, less than about 275 mg, less than about 270 mg, less than about 265 mg, less than about 260 mg, less than about 255 mg, less than about 250 mg, less than about 245 mg, less than about 240 mg, less than about 235 mg, less than about 230 mg, less than about 225 mg, less than about 220 mg, less than about 215 mg, less than about 210 mg, less than about 205 mg, less than about 200 mg, less than about 195 mg, less than about 190 mg, less than about 185 mg, less than about 180 mg, less than about 175 mg, less than about 170 mg, less than about 165 mg, less than about 160 mg, less than about 150 mg, less than about 145 mg, less than about 140 mg, less than about 135 mg, less than about 130 mg, less than about 125 mg, less than about 120 mg, less than about 115 mg, less than about 110 mg, less than about 105 mg, less than about 100 mg, less than about 95 mg, less than about 90 mg, less than about 85 mg, less than about 80 mg, less than about 75 mg, less than about 70 mg, less than about 65 mg, less than about 60 mg, less than about 55 mg, less than about 50 mg, less than about 45 mg, less than about 40 mg, less than about 35 mg, less than about 30 mg, less than about 25 mg, or less than about 20 mg of an oligomeric compound disclosed herein. The dosage unit may contain more than about 5 mg or more than about 10 mg of the oligomeric compound.

In certain embodiments, the oligomeric compound is present in the dosage unit at an amount that is less than 300 mg, less than 295 mg, less than 290 mg, less than 285 mg, less than 280 mg, less than 275 mg, less than 270 mg, less than 265 mg, less than 260 mg, less than 255 mg, less than 250 mg, less than 245 mg, less than 240 mg, less than 235 mg, less than 230 mg, less than 225 mg, less than 220 mg, less than 215 mg, less than 210 mg, less than 205 mg, less than 200 mg, less than 195 mg, less than 190 mg, less than 185 mg, less than 180 mg, less than 175 mg, less than 170 mg, less than 165 mg, less than 160 mg, less than 150 mg, less than 145 mg, less than 140 mg, less than 135 mg, less than 130 mg, less than 125 mg, less than 120 mg, less than 115 mg, less than 110 mg, less than 105 mg, less than 100 mg, less than 95 mg, less than 90 mg, less than 85 mg, less than 80 mg, less than 75 mg, less than 70 mg, less than 65 mg, less than 60 mg, less than 55 mg, less than 50 mg, less than 45 mg, less than 40 mg, less than 35 mg, less than 30 mg, less than 25 mg, or

less than 20 mg of an oligomeric compound disclosed herein. The dosage unit may contain more than 5 mg or more than 10 mg of the oligomeric compound.

In certain embodiments, the oligomeric compound is present in the dosage unit at an amount that is at least about 10 mg, at least about 15 mg, at least about 20 mg, at least about 25 mg, at least about 30 mg, at least about 35 mg, at least about 40 mg, at least about 45 mg, at least about 50 mg, at least about 55 mg, at least about 60 mg, at least about 65 mg, at least about 70 mg, at least about 75 mg, at least about 80 mg, at least about 85 mg, at least about 90 mg, at least about 95 mg, at least about 100 mg, at least about 105 mg, at least about 115 mg, at least about 120 mg, at least about 125 mg, at least about 130 mg, at least about 135 mg, at least about 140 mg, at least about 145 mg, or at least about 150 mg of an oligomeric compound disclosed herein.

In certain embodiments, the oligomeric compound is present in the dosage unit at an amount that is at least 10 mg, at least 15 mg, at least 20 mg, at least 25 mg, at least 30 mg, at least 35 mg, at least 40 mg, at least 45 mg, at least 50 mg, at least 55 mg, at least 60 mg, at least 65 mg, at least 70 mg, at least 75 mg, at least 80 mg, at least 85 mg, at least 90 mg, at least 95 mg, at least about 100 mg, at least 105 mg, at least 115 mg, at least 120 mg, at least 125 mg, at least 130 mg, at least 135 mg, at least 140 mg, at least 145 mg, or at least 150 mg of an oligomeric compound disclosed herein

In certain embodiments, pharmaceutical compositions disclosed herein are provided as a volume of a solution comprising an oligomeric compound and a pharmaceutically acceptable carrier or diluent. In certain embodiments, the solution consists or consists essentially of an oligomeric compound disclosed herein and a pharmaceutically acceptable carrier or diluent. The volume may be provided in a suitable container, such as a vial or syringe. Since pharmaceutical compositions disclosed herein may be amenable to self-administration, the syringe may be a pre-filled syringe, an auto-injector syringe, or a combination thereof. For example, a dosage unit described herein may be provided as a fixed volume in a syringe for convenient administration. In certain embodiments, the volume of the solution is 0.1 ml, 0.2 ml, 0.3 ml, 0.4 ml, 0.5 ml, 0.6 ml, 0.7 ml, 0.8 ml, 0.9 ml, 1.0 ml, 1.1 ml, 1.2 ml, 1.3 ml, 1.4 ml, 1.5 ml, 1.6 ml, 1.7 ml, 1.8 ml, 1.9 ml, or 2.0 ml. In certain embodiments, the volume of the solution is about 0.1 ml, about 0.2 ml, about 0.3 ml, about 0.4 ml, about 0.5 ml, about 0.6 ml, about 0.7 ml, about 0.8 ml, about 0.9 ml, about 1.0 ml, about 1.1 ml, about 1.2 ml, about 1.3 ml, about 1.4 ml, about 1.5 ml, about 1.6 ml, about 1.7 ml, about 1.8 ml, about 1.9 ml, or about 2.0 ml. In certain embodiments, the volume of the solution is less than 1.0 ml, less than 1.5 ml, or 2.0 ml. In certain embodiments, the volume of the solution is less than 1.0 ml. A volume of less than 2.0 ml may be useful to reduce or avoid injection pain, adverse events at the injection site, and injection site leakage.

In certain embodiments, pharmaceutical compositions disclosed herein are provided as a volume of a solution comprising an oligomeric compound and a pharmaceutically acceptable carrier or diluent, wherein the volume of the solution is 0.1 ml to 1.5 ml, 0.1 ml to 1.4 ml, 0.1 ml to 1.3 ml, 0.1 ml to 1.2 ml, 0.1 ml to 1.1 ml, 0.1 ml to 1.0 ml, 0.1 ml to 0.9 ml, 0.1 ml to 0.8 ml, 0.1 ml to 0.7 ml, 0.1 ml to 0.6 ml, 0.1 ml to 0.5 ml, 0.1 ml to 0.4 ml, 0.1 ml to 0.3 ml, 0.1 ml to 0.2 ml, 0.2 ml to 1.5 ml, 0.2 ml to 1.4 ml, 0.2 ml to 1.3 ml,

0.2 ml to 1.2 ml, 0.2 ml to 1.1 ml, 0.2 ml to 1.0 ml, 0.2 ml to 0.9 ml, 0.2 ml to 0.8 ml, 0.2 ml to 0.7 ml, 0.2 ml to 0.6 ml, 0.2 ml to 0.5 ml, 0.2 ml to 0.4 ml, 0.2 ml to 0.3 ml, 0.3 ml to 1.5ml, 0.3 ml to 1.4 ml, 0.3 ml to 1.3 ml, 0.3 ml to 1.2 ml, 0.3 ml to 1.1 ml, 0.3 ml to 1.0 ml, 0.3 ml to 0.9 ml, 0.3 ml to 0.8 ml, 0.3 ml to 0.7 ml, 0.3 ml to 0.6 ml, 0.3 ml to 0.5 ml, 0.3 ml to 0.4 ml, 0.4 ml to 1.5 ml, 0.4 ml to 1.4 ml, 0.4 ml to 1.3 ml, 0.4 ml to 1.2 ml, 0.4 ml to 1.1 ml, 0.4 ml to 1.0 ml, 0.4 ml to 0.9 ml, 0.4 ml to 0.8 ml, 0.4 ml to 0.7 ml, 0.4 ml to 0.6 ml, 0.4 ml to 0.5 ml, 0.5 ml to 1.5 ml, 0.5 ml to 1.4 ml, 0.5 ml to 1.3 ml, 0.5. ml to 1.2 ml, 0.5 ml to 1.1 ml, 0.5 ml to 1.0 ml, 0.5 ml to 0.9 ml, 0.5 ml to 0.8 ml, 0.5 ml to 0.7 ml, 0.5 ml to 0.6 ml, 0.6 ml to 1.5 ml, 0.6 ml to 1.4 ml, 0.6 mo to 1.3 ml, 0.6 ml to 1.2 ml, 0.6 ml to 1.1 ml, 0.6 ml to 1.0 ml, 0.6 ml to 0.9 ml, 0.6 ml to 0.8 ml, 0.6 ml to 0.7 ml, 0.7 ml, to 1.5 ml, 0.7 ml to 1.4 ml, 0.7 ml to 1.3 ml, 0.7 ml to 1.2 ml, 0.7 ml to 1.1 ml, 0.7 ml to 1.0 ml, 0.7 ml to 0.9 ml, 0.7 ml to 0.8 ml, 0.8 ml to 1.5 ml, 0.8 ml to 1.4 ml, 0.8 ml to 1.3 ml, 0.8 ml to 1.2 ml, 0.8 ml to 1.1 ml, 0.8 ml to 1.0 ml. 0.8 ml to 0.9 ml, 0.9 ml, to 1.5 ml, 0.9 ml to 1.4 ml, 0.9 ml to 1.3 ml, 0.9 ml to 1.2 ml, 0.9 ml, to 1.1 ml, 0.9 ml to 1.0 ml, 1.0 ml to 1.5 ml, 1.0 ml to 1.4 ml, 1.0 ml to 1.3 ml, 1.0 ml to 1.2 ml, 1.0 ml to 1.1 ml, 1.1 ml to 1.5 ml, 1.1 ml to 1.4 ml, 1.1 ml to 1.3 ml, 1.1 ml to 1.2 ml, 1.2 ml to 1.5 ml, 1.2 ml to 1.4 ml, 1.2 ml to 1.3 ml, 1.3 ml to 1.5 ml, 1.3 ml to 1.4 ml, 1.4 ml to, and 1.5ml.

In certain embodiments, pharmaceutical compositions comprise a solution of an oligomeric compound disclosed herein in a pharmaceutically acceptable carrier or diluent at a concentration of 5 mg/ml, 10 mg/ml, 15 mg/ml, 20 mg/ml, 25 mg/ml, 30 mg/ml, 35 mg/ml, 40 mg/ml, 45 mg/ml, 50 mg/ml, 55 mg/ml, 60 mg/ml, 65 mg/ml, 70 mg/ml, 75 mg/ml, 80 mg/ml, 85 mg/ml, 90 mg/ml, 95 mg/ml, 100 mg/ml, 105 mg/ml, 110 mg/ml, 115 mg/ml, 120 mg/ml, 125 mg/ml, 130 mg/ml, 135 mg/ml, 140 mg/ml, 145 mg/ml, 150 mg/ml, 155 mg/ml, or 160 mg/ml. In certain embodiments, pharmaceutical compositions comprise a solution of an oligomeric compound disclosed herein in a pharmaceutically acceptable carrier or diluent at a concentration of about 5 mg/ml, about 10 mg/ml, about 15 mg/ml, about 20 mg/ml, about 25 mg/ml, about 30 mg/ml, about 35 mg/ml, about 40 mg/ml, about 45 mg/ml, about 50 mg/ml, about 55 mg/ml, about 60 mg/ml, about 65 mg/ml, about 70 mg/ml, about 75 mg/ml, about 80 mg/ml, about 85 mg/ml, about 90 mg/ml, about 95 mg/ml, about 100 mg/ml, about 105 mg/ml, about 110 mg/ml, about 115 mg/ml, about 120 mg/ml, about 125 mg/ml, about 130 mg/ml, about 135 mg/ml, about 140 mg/ml, about 145 mg/ml, about 150 mg/ml, about 155 mg/ml, or about 160 mg/ml.

In certain embodiments, pharmaceutical compositions comprise a solution of an oligomeric compound disclosed herein in a pharmaceutically acceptable carrier or diluent at a concentration of 20 mg/ml, 21 mg/ml, 22 mg/ml, 23 mg/ml, 24 mg/ml, 25 mg/ml, 26 mg/ml, 27 mg/ml, 28 mg/ml, 29 mg/ml, 30 mg/ml, 31 mg/ml, 32 mg/ml, 33 mg/ml, 34 mg/ml, 35 mg/ml, 36 mg/ml, 37 mg/ml, 38 mg/ml, 39 mg/ml, 40 mg/ml, 41 mg/ml, 42 mg/ml, 43 mg/ml, 44 mg/ml, 45 mg/ml, 46 mg/ml, 47 mg/ml, 48 mg/ml, 49 mg/ml, 50 mg/ml, 51 mg/ml, 52 mg/ml, 53 mg/ml, 54 mg/ml, 55 mg/ml, 56 mg/ml, 57 mg/ml, 58 mg/ml, 59 mg/ml, 60 mg/ml, 61 mg/ml, 62 mg/ml, 63 mg/ml, 64 mg/ml, 65 mg/ml, 66 mg/ml, 67 mg/ml, 68 mg/ml, 69 mg/ml, 70 mg/ml, 71 mg/ml, 72 mg/ml, 73 mg/ml, 74 mg/ml, 75 mg/ml, 76 mg/ml, 77 mg/ml, 78 mg/ml, 79 mg/ml, 80 mg/ml, 81 mg/ml, 82 mg/ml, 83 mg/ml, 84 mg/ml, 85 mg/ml, 86 mg/ml, 87 mg/ml, 88 mg/ml, 89 mg/ml, 90

mg/ml, 91 mg/ml, 92 mg/ml, 93 mg/ml, 94 mg/ml, 95 mg/ml, 96 mg/ml, 97 mg/ml, 98 mg/ml, 99 mg/ml, 100 mg/ml, 101 mg/ml, 102 mg/ml, 103 mg/ml, 104 mg/ml, 105 mg/ml, 106 mg/ml, 107 mg/ml, 108 mg/ml, 109 mg/ml, 110 mg/ml, 111 mg/ml, 112 mg/ml, 113 mg/ml, 114 mg/ml, 115 mg/ml, 116 mg/ml, 117 mg/ml, 118 mg/ml, 119 mg/ml, 120 mg/ml, 121 mg/ml, 122 mg/ml, 123 mg/ml, 124 mg/ml, 125 mg/ml, 126 mg/ml, 127 mg/ml, 128 mg/ml, 129 mg/ml, 130 mg/ml, 131 mg/ml, 132 mg/ml, 133 mg/ml, 134 mg/ml, 135 mg/ml, 136 mg/ml, 137 mg/ml, 138 mg/ml, 139 mg/ml, and 140 mg/ml. In certain embodiments, the oligomeric compound is present in the dosage unit at an amount selected from about 20 mg/ml, about 21 mg/ml, about 22 mg/ml, about 23 mg/ml, about 24 mg/ml, about 25 mg/ml, about 26 mg/ml, about 27 mg/ml, about 28 mg/ml, about 29 mg/ml, about 30 mg/ml, about 31 mg/ml, about 32 mg/ml, about 33 mg/ml, about 34 mg/ml, about 35 mg/ml, about 36 mg/ml, about 37 mg/ml, about 38 mg/ml, about 39 mg/ml, about 40 mg/ml, about 41 mg/ml, about 42 mg/ml, about 43 mg/ml, about 44 mg/ml, about 45 mg/ml, about 46 mg/ml, about 47 mg/ml, about 48 mg/ml, about 49 mg/ml, about 50 mg/ml, about 51 mg/ml, about 52 mg/ml, about 53 mg/ml, about 54 mg/ml, about 55 mg/ml, about 56 mg/ml, about 57 mg/ml, about 58 mg/ml, about 59 mg/ml, about 60 mg/ml, about 61 mg/ml, about 62 mg/ml, about 63 mg/ml, about 64 mg/ml, about 65 mg/ml, about 66 mg/ml, about 67 mg/ml, about 68 mg/ml, about 69 mg/ml, about 70 mg/ml, about 71 mg/ml, about 72 mg/ml, about 73 mg/ml, about 74 mg/ml, about 75 mg/ml, about 76 mg/ml, about 77 mg/ml, about 78 mg/ml, about 79 mg/ml, about 80 mg/ml, about 81 mg/ml, about 82 mg/ml, about 83 mg/ml, about 84 mg/ml, about 85 mg/ml, about 86 mg/ml, about 87 mg/ml, about 88 mg/ml, about 89 mg/ml, about 90 mg/ml, about 91 mg/ml, about 92 mg/ml, about 93 mg/ml, about 94 mg/ml, about 95 mg/ml, about 96 mg/ml, about 97 mg/ml, about 98 mg/ml, about 99 mg/ml, about 100 mg/ml, about 101 mg/ml, about 102 mg/ml, about 103 mg/ml, about 104 mg/ml, about 105 mg/ml, about 106 mg/ml, about 107 mg/ml, about 108 mg/ml, about 109 mg/ml, about 110 mg/ml, about 111 mg/ml, about 112 mg/ml, about 113 mg/ml, about 114 mg/ml, about 115 mg/ml, about 116 mg/ml, about 117 mg/ml, about 118 mg/ml, about 119 mg/ml, about 120 mg/ml, about 121 mg/ml, about 122 mg/ml, about 123 mg/ml, about 124 mg/ml, about 125 mg/ml, about 126 mg/ml, about 127 mg/ml, about 128 mg/ml, about 129 mg/ml, about 130 mg/ml, about 131 mg/ml, about 132 mg/ml, about 133 mg/ml, about 134 mg/ml, about 135 mg/ml, about 136 mg/ml, about 137 mg/ml, about 138 mg/ml, about 139 mg/ml, and about 140 mg/ml.

In certain embodiments, pharmaceutical compositions comprise a solution of an oligomeric compound disclosed herein in a pharmaceutically acceptable carrier or diluent at a concentration of 20 mg/ml to 180 mg/ml, 20 mg/ml to 170 mg, 20 mg/ml to 160 mg/ml, 20 mg/ml to 150 mg/ml, 20 mg/ml to 140 mg/ml, 20 mg/ml to 130 mg/ml, 20 mg/ml to 120 mg/ml, 20 mg/ml to 110 mg/ml, 20 mg/ml to 100 mg/ml, 20 mg/ml to 90 mg/ml, 20 mg/ml to 80 mg/ml, 20 mg/ml to 70 mg/ml, 20 mg/ml to 60 mg/ml, 20 mg/ml to 50 mg/ml, 20 mg/ml to 40 mg/ml, 20 mg/ml to 30 mg/ml, 30 mg/ml to 180 mg/ml, 30 mg/ml to 170 mg, 30 mg/ml to 160 mg/ml, 30 mg/ml to 150 mg/ml, 30 mg/ml to 140 mg/ml, 30 mg/ml to 130 mg/ml, 30 mg/ml to 120 mg/ml, 30 mg/ml to 110 mg/ml, 30 mg/ml to 100 mg/ml, 30 mg/ml to 90 mg/ml, 30 mg/ml to 80 mg/ml, 30 mg/ml to 70 mg/ml, 30 mg/ml to 60 mg/ml, 30 mg/ml to 50 mg/ml, 30 mg/ml to 40 mg/ml, 40 mg/ml to

180 mg/ml, 40 mg/ml to 170 mg, 40 mg/ml to 160 mg/ml, 40 mg/ml to 150 mg/ml, 40 mg/ml to 140 mg/ml, 40 mg/ml to 130 mg/ml, 40 mg/ml to 120 mg/ml, 40 mg/ml to 110 mg/ml, 40 mg/ml to 100 mg/ml, 40 mg/ml to 90 mg/ml, 40 mg/ml to 80 mg/ml, 40 mg/ml to 70 mg/ml, 40 mg/ml to 60 mg/ml, 40 mg/ml to 50 mg/ml, 50 mg/ml to 180 mg/ml, 50 mg/ml to 170 mg, 50 mg/ml to 160 mg/ml, 50 mg/ml to 150 mg/ml, 50 mg/ml to 140 mg/ml, 50 mg/ml to 130 mg/ml, 50 mg/ml to 120 mg/ml, 50 mg/ml to 110 mg/ml, 50 mg/ml to 100 mg/ml, 50 mg/ml to 90 mg/ml, 50 mg/ml to 80 mg/ml, 50 mg/ml to 70 mg/ml, 50 mg/ml to 60 mg/ml, 60 mg/ml to 180 mg/ml, 60 mg/ml to 170 mg, 60 mg/ml to 160 mg/ml, 60 mg/ml to 150 mg/ml, 60 mg/ml to 140 mg/ml, 60 mg/ml to 130 mg/ml, 60 mg/ml to 120 mg/ml, 60 mg/ml to 110 mg/ml, 60 mg/ml to 100 mg/ml, 60 mg/ml to 90 mg/ml, 60 mg/ml to 80 mg/ml, 60 mg/ml to 70 mg/ml, 70 mg/ml to 180 mg/ml, 70 mg/ml to 170 mg, 70 mg/ml to 160 mg/ml, 70 mg/ml to 150 mg/ml, 70 mg/ml to 140 mg/ml, 70 mg/ml to 130 mg/ml, 70 mg/ml to 120 mg/ml, 70 mg/ml to 110 mg/ml, 70 mg/ml to 100 mg/ml, 70 mg/ml to 90 mg/ml, 70 mg/ml to 80 mg/ml, 80 mg/ml to 180 mg/ml, 80 mg/ml to 170 mg, 80 mg/ml to 160 mg/ml, 80 mg/ml to 150 mg/ml, 80 mg/ml to 140 mg/ml, 80 mg/ml to 130 mg/ml, 80 mg/ml to 120 mg/ml, 80 mg/ml to 110 mg/ml, 80 mg/ml to 100 mg/ml, 80 mg/ml to 90 mg/ml, 90 mg/ml to 180 mg/ml, 90 mg/ml to 170 mg, 90 mg/ml to 160 mg/ml, 90 mg/ml to 150 mg/ml, 90 mg/ml to 140 mg/ml, 90 mg/ml to 130 mg/ml, 90 mg/ml to 120 mg/ml, 90 mg/ml to 110 mg/ml, 90 mg/ml to 100 mg/ml, 100 mg/ml to 180 mg/ml, 100 mg/ml to 170 mg, 100 mg/ml to 160 mg/ml, 100 mg/ml to 150 mg/ml, 100 mg/ml to 140 mg/ml, 100 mg/ml to 130 mg/ml, 100 mg/ml to 120 mg/ml, 100 mg/ml to 110 mg/ml, 110 mg/ml to 180 mg/ml, 110 mg/ml to 170 mg, 110 mg/ml to 160 mg/ml, 110 mg/ml to 150 mg/ml, 110 mg/ml to 140 mg/ml, 110 mg/ml to 130 mg/ml, 110 mg/ml to 120 mg/ml, 120 mg/ml to 180 mg/ml, 120 mg/ml to 170 mg, 120 mg/ml to 160 mg/ml, 120 mg/ml to 150 mg/ml, 120 mg/ml to 140 mg/ml, 120 mg/ml to 130 mg/ml, 130 mg/ml to 180 mg/ml, 130 mg/ml to 170 mg, 130 mg/ml to 160 mg/ml, 130 mg/ml to 150 mg/ml, 130 mg/ml to 140 mg/ml, 140 mg/ml to 180 mg/ml, 140 mg/ml to 170 mg/ml, 140 mg/ml to 160 mg/ml, 140 mg/ml to 150 mg/ml, 150 mg/ml to 180 mg/ml, 150 mg/ml to 170 mg/ml, 150 mg/ml to 160 mg/ml, 160 mg/ml to 180 mg/ml, 160 mg/ml to 170 mg/ml, or 170 mg/ml to 180 mg/ml.

In certain embodiments, pharmaceutical compositions disclosed herein comprise a sterile lyophilized oligomeric compound that can be reconstituted with a suitable diluent for injection. In certain embodiments, pharmaceutical compositions disclosed herein consist or consist essentially of a sterile lyophilized oligomeric compound that can be reconstituted with a suitable diluent for injection. In certain embodiments, the reconstituted product is administered as a subcutaneous injection after dilution. In certain embodiments, a sterile lyophilized oligomeric compound may consist of the oligomeric compound which has been prepared in distilled water for injection, adjusted to pH 7.0-9.0 with acid or base during preparation, and then lyophilized. The sterile lyophilized oligomeric compound may be packaged in a Type I, clear glass vial (ammonium sulfate-treated), stoppered with a bromobutyl rubber closure and sealed with an aluminum FLIP-OFF® overseal. In certain embodiments, the sterile lyophilized oligomeric compound comprises Compound

No. 957943. In certain embodiments, the sterile lyophilized oligomeric compound consists or consists essentially of Compound No. 957943.

VIII. Certain Dosing Regimens

Pharmaceutical compositions disclosed herein may be suitable for acute treatment, temporary treatment, ongoing (prophylactic) treatment, chronic treatment, or a combination thereof. In certain embodiments, methods comprise continually administering a pharmaceutical composition disclosed herein as a prophylactic measure. In certain embodiments, methods comprise temporarily administering a pharmaceutical composition disclosed herein. For example, methods may comprise administering a pharmaceutical composition disclosed herein to an animal within 24 hours of the animal experiencing a thromboembolic event. In certain embodiments, methods comprise administering a pharmaceutical composition disclosed herein to an animal before surgery, during surgery, after surgery, or a combination thereof. In certain embodiments, methods comprise prophylactically administering a pharmaceutical composition disclosed herein on a monthly basis to an animal with a FXI associated disease or condition who is at risk for a thrombotic event. In certain embodiments, the pharmaceutical composition comprises Compound No. 957943. In certain embodiments, the pharmaceutical composition consists or consists essentially of Compound No. 957943 and a pharmaceutically acceptable carrier or diluent.

In certain embodiments, pharmaceutical compositions disclosed herein are useful for treating an animal with a FXI associated disease or condition. In certain embodiments, methods comprise administering a pharmaceutical composition disclosed herein to an animal only once. In certain embodiments, methods comprise administering a pharmaceutical composition disclosed herein to an animal at least twice. In certain embodiments, methods comprise administering a pharmaceutical composition disclosed herein at least 3, at least 4, at least 5, at least 6, at least 8, or at least 10 times. In certain embodiments, methods comprise administering a pharmaceutical composition disclosed herein less than 20 times, less than 15 times, less than 10 times, or less than 5 times.

In certain embodiments, methods comprise administering to an animal a first dose and a second dose of an oligomeric compound disclosed herein. In certain embodiments, the first dose and the second dose are the same. In certain embodiments, the first dose and the second dose are different. In certain embodiments, the first dose is greater than the second dose. In certain embodiments, the second dose is greater than the first dose. In certain embodiments, the first dose is at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 100% greater than the second dose. In certain embodiments, the second dose is at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 100% greater than the first dose. In certain embodiments, the first dose and the second dose are separated by 5, 10, 15, 20, 25, 30, 35, or 40 days. In certain embodiments, the first dose and the second dose are separated by 1, 2, 3, 4, 5, or 6 months. In certain embodiments, the first dose and the second dose are separated by 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30,

31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 days. In certain embodiments, the first dose and the second dose are separated by 20 to 40 days, 22 to 38 days, 24 to 36 days, 26 to 34 days, 27 to 32 days, 28 to 32 days, or 29 to 31 days. In certain embodiments, the first dose and the second dose are separated by 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 weeks. In certain embodiments, the first dose and the second dose are separated by 1 to 2 days, 2 to 4 days, 3 to 5 days, 4 to 6 days, 5 to 7 days, 6 to 8 days, 7 to 9 days, 8 to 10 days, 9 to 11 days, 10 to 12 days, 11 to 13 days, 12 to 14 days, 13 to 15 days, 14 to 16 days, 15 to 17 days, 16 to 18 days, 17 to 19 days, or 18 to 20 days.

In certain embodiments, methods comprise administering a pharmaceutical composition disclosed herein monthly or about monthly. In certain embodiments, methods comprise administering a composition disclosed herein to an animal monthly or about monthly for at least two months, at least three months, at least four months, at least five months, or at least six months. In certain embodiments, methods comprise administering a pharmaceutical composition disclosed herein weekly or about weekly. In certain embodiments, methods comprise administering a composition disclosed herein to an animal weekly or about weekly for less than 2 weeks, less than 3 weeks, less than 4 weeks, less than 5 weeks, less than 6 weeks, less than 8 week, less than 12 weeks, less than 16 weeks, or less than 20 weeks.

In certain embodiments, methods comprise administering an oligomeric compound according to a first dosing regimen and subsequently administering the oligomeric compound according to a second dosing regimen. In certain embodiments, the first dosing regimen comprises administering the oligomeric compound at a first dose and at a first frequency and the second dosing regimen comprises administering the oligomeric compound at a second dose and at a second frequency. In certain embodiments, the first frequency is greater than the second frequency. By way of non-limiting example, the first frequency may be greater than once monthly (2 times, 3 times or 4 times per month) and the second frequency may be once monthly. In certain embodiments, the first frequency is less than the second frequency. In certain embodiments, the first dose is greater than the second dose and the first frequency is greater than the second frequency. In certain embodiments, the first dose is less than the second dose and the first frequency is greater than the second frequency. In certain embodiments, the first dose is greater than the second dose and the first frequency is less than the second frequency. In certain embodiments, the first dose is less than the second dose and the first frequency is less than the second frequency. In certain embodiments, the first dose and the second dose are the same, and the first frequency is greater than the second frequency. In certain embodiments, the first dose and the second dose are the same and the first frequency is less than the second frequency. In certain embodiments, the first dose is greater than the second dose, and the first frequency and the second frequency are the same. In certain embodiments, the first dose is less than the second dose and the first frequency and the second frequency are the same. In certain embodiments, at least one of the first frequency and the second frequency are selected from about every 5, about every 10, about every 15, about every 20, about every 25, about every 30, about every 35, or about every 40 days. In certain embodiments, at least one of the first frequency and the second frequency is monthly. In certain embodiments, at least one of the first frequency

and the second frequency is weekly. In certain embodiments, the first dose is at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 100% greater than the second dose. In certain embodiments, the second dose is at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 100% greater than the first dose.

In certain embodiments, methods comprise a human subject self-administering a pharmaceutical composition disclosed herein. In certain embodiments, methods disclosed herein comprise a human subject self-administering a pharmaceutical composition disclosed herein by subcutaneous injection. In certain embodiments, methods disclosed herein comprise self-administering monthly. In general, pharmaceutical compositions disclosed herein are prepared for subcutaneous administration and a single dose can be provided with a single injection, which makes these pharmaceutical compositions amenable to self-administration. A single injection is possible because oligomeric compounds disclosed herein are highly potent and only a small amount needs to be dissolved in a small volume of a carrier or diluent to provide a dosage unit. Due to the potency and efficacy of oligomeric compounds disclosed herein, in certain embodiments, the animal may only need to receive a dose on a monthly basis to experience therapeutic effects. Such dosing regimens that allow for self-administration on a monthly basis are desirable to patients when compared to dosing regimens of other therapies aimed to treat subjects with FXI associated conditions and diseases, the latter of which may require in-clinic intravenous injection and more frequent administration.

In certain embodiments, administration of a therapeutically effective amount of a pharmaceutical composition as described herein is accompanied by monitoring an amount of a FXI RNA, an amount of a FXI protein, and/or FXI activity in the plasma or serum of an animal, to determine the animal's response to administration of the pharmaceutical composition. An animal's response to administration of the pharmaceutical composition may be used by a physician to determine the amount and duration of therapeutic intervention.

IX. Certain Combination Therapies

In certain embodiments, methods comprise co-administering one or more pharmaceutical compositions described herein with one or more other pharmaceutical agents. In certain embodiments, such one or more other pharmaceutical agents are designed to treat the same disease or condition as the one or more pharmaceutical compositions described herein. In certain embodiments, such one or more other pharmaceutical agents are designed to treat a different disease or condition as the one or more pharmaceutical compositions described herein. In certain embodiments, such one or more other pharmaceutical agents are designed to treat an undesired side effect of one or more pharmaceutical compositions described herein. In certain embodiments, methods comprise co-administering one or more pharmaceutical compositions described herein with one or more other pharmaceutical agents to treat an undesired effect of the other pharmaceutical composition. In certain embodiments, methods comprise co-administering one or more

pharmaceutical compositions described herein with one or more other pharmaceutical agents to produce a combinational effect. In certain embodiments, methods comprise co-administering one or more pharmaceutical compositions described herein with one or more other pharmaceutical agents to produce a synergistic effect. In certain embodiments, the pharmaceutical composition comprises Compound No. 957943. In certain embodiments, the pharmaceutical composition consists or consists essentially of Compound No. 957943 and a pharmaceutically acceptable carrier or diluent.

In certain embodiments, methods comprise co-administering one or more pharmaceutical compositions described herein with one or more other pharmaceutical agents at the same time. In certain embodiments, methods comprise co-administering one or more pharmaceutical compositions described herein with one or more other pharmaceutical agents at different times. In certain embodiments, one or more pharmaceutical compositions described herein and one or more other pharmaceutical agents are prepared together in a single formulation. In certain embodiments, one or more pharmaceutical compositions described herein and one or more other pharmaceutical agents are prepared separately.

In certain embodiments, pharmaceutical agents that may be co-administered with a pharmaceutical composition described herein include anticoagulant or antiplatelet agents. In certain embodiments, pharmaceutical agents that may be co-administered with a pharmaceutical composition described herein include NSAID/Cyclooxygenase inhibitors, such as, aspirin. In certain embodiments, pharmaceutical agents that may be co-administered with a pharmaceutical composition described herein include adenosine diphosphate (ADP) receptor inhibitors, such as, clopidogrel (PLAVIX) and ticlopidine (TICLID). In certain embodiments, pharmaceutical agents that may be co-administered with a pharmaceutical composition described herein include phosphodiesterase inhibitors, such as, cilostazol (PLETAL). In certain embodiments, pharmaceutical agents that may be co-administered with a pharmaceutical composition described herein include, glycoprotein IIB/IIIA inhibitors, such as, abciximab (REOPRO), eptifibatide (INTEGRILIN), tirofiban (AGGRASTAT), and defibrotide. In certain embodiments, pharmaceutical agents that may be co-administered with a pharmaceutical composition described herein include, adenosine reuptake inhibitors, such as, dipyridamole (PERSANTINE). In certain embodiments, pharmaceutical agents that may be co-administered with a pharmaceutical composition described herein include, but are not limited to, warfarin (and related coumarins), heparin, direct thrombin inhibitors (such as lepirudin, bivalirudin), apixaban, LOVENOX (enoxaparin), and small molecular compounds that interfere directly with the enzymatic action of particular coagulation factors (*e.g.* rivaroxaban, which interferes with Factor Xa). In certain embodiments, the anticoagulant or antiplatelet agent is administered prior to administration of a pharmaceutical composition described herein. In certain embodiments, the anticoagulant or antiplatelet agent is administered following administration of a pharmaceutical composition described herein. In certain embodiments the anticoagulant or antiplatelet agent is administered at the same time as a pharmaceutical composition described herein. In certain embodiments, the dosage unit of a co-administered anticoagulant or antiplatelet agent is the same as the dosage unit that would be administered if the anticoagulant or antiplatelet

agent was administered alone. In certain embodiments the dosage unit of a co-administered anticoagulant or antiplatelet agent is lower than the dosage unit that would be administered if the anticoagulant or antiplatelet agent was administered alone. In certain embodiments the dosage unit of a co-administered anticoagulant or antiplatelet agent is greater than the dosage unit that would be administered if the anticoagulant or antiplatelet agent was administered alone.

In certain embodiments, methods may comprise co-administering a pharmaceutical composition described herein with an anti-inflammatory agent. In certain embodiments, the anti-inflammatory agent modifies a symptom of the inflammatory disease or condition. In certain embodiments, the anti-inflammatory agent modifies progression of the inflammatory disease or condition. Non-limiting examples of inflammatory disesases and conditions are autoimmune diseases (*e.g.* arthritis, colitis or diabetes), trauma, surgery, sepsis, allergic inflammation, and asthma. Non-limiting examples of anti-inflammatory agents include, but are not limited to, methotrexate, abatacept, infliximab, cyclophosphamide, azathioprine, corticosteroids, cyclosporin A, aminosalicylates, sulfasalazine, hydroxychloroquine, leflunomide, etanercept, efalizumab, 6-mercapto-purine (6-MP), and tumor necrosis factor-alpha (TNFalpha), and other cytokine blockers or antagonists. In certain embodiments, the anti-inflammatory agent comprises a non-steroidal anti-inflammatory drug (NSAID). In certain embodiments, NSAIDs reduce inflammatory reactions in an animal. NSAIDS include, but are not limited to, acetyl salicylic acid, choline magnesium salicylate, diflunisal, magnesium salicylate, salsalate, sodium salicylate, diclofenac, etodolac, fenoprofen, flurbiprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, naproxen, nabumetone, phenylbutazone, piroxicam, sulindac, tolmetin, acetaminophen, ibuprofen, Cox-2 inhibitors, meloxicam and tramadol. In certain embodiments, methods comprise administering a pharmaceutical composition disclosed herein and an anti-inflammatory agent concomitantly or sequentially. In certain embodiments, methods comprise administering the anti-inflammatory agent prior to administering the pharmaceutical composition described herein. In certain embodiments, methods comprise administering the anti-inflammatory agent after administering a pharmaceutical composition described herein. In certain embodiments, methods comprise administering the anti-inflammatory agent and a pharmaceutical composition described herein at the same time. In certain embodiments, the dosage unit of a co-administered anti-inflammatory agent is the same as the dosage unit that would be administered if the anti-inflammatory agent was administered alone. In certain embodiments the dosage unit of a co-administered anti-inflammatory agent is lower than the dosage unit that would be administered if the anti-inflammatory agent was administered alone. In certain embodiments the dosage unit of a co-administered anti-inflammatory agent is greater than the dosage unit that would be administered if the anticoagulant or antiplatelet agent was administered alone.

In certain embodiments, the co-administration of a second pharmaceutical agent enhances the anticoagulant or anti-inflammatory effect of a pharmaceutical composition described herein, such that co-administration of the two results in an anticoagulant or anti-inflammatory effect that is greater than the effect of administering the pharmaceutical composition described herein. In certain embodiments, the co-

administration results in anticoagulant or anti-inflammatory effects that are additive of the effects of the two when administered alone. In certain embodiments, the co-administration results in anticoagulant or anti-inflammatory effects that are supra-additive of the effects of the two when administered alone. In certain embodiments, co-administration of a second pharmaceutical agent increases an antithrombotic activity or anti-inflammatory activity of the pharmaceutical composition relative to that provided by the pharmaceutical composition alone, without increased bleeding risk.

In certain embodiments, methods comprise co-administering a pharmaceutical composition described herein and an antiplatelet therapy to an animal in need thereof. In certain embodiments, the animal in need thereof may be an animal having a condition selected from thromboembolism, atrial fibrillation, a heart valve disorder, valvular heart disease, stroke, coronary artery disease (CAD), and a mechanical heart valve, and a combination thereof. In certain embodiments, administering a pharmaceutical composition described herein in combination with an antiplatelet therapy results in little to no detectable increase in risk of bleeding as compared to antiplatelet therapy alone. In certain embodiments, the risk profile or risk indications are unchanged over antiplatelet therapy alone.

In certain embodiments, methods comprise administering a pharmaceutical composition described herein to a dialysis patient, including but not limited to an animal with end stage renal disease (ESRD) or chronic kidney disease (CKD), wherein the animal is co-administered at least one pharmaceutical agent selected from heparin, erythropoietin, darbopoetin, iron, Vitamin D or analogues thereof, phosphate binders, and a combination thereof. In certain embodimenst, the animal receives dialysis. In certain embodiments, the pharmaceutical agent is administered at a dose that does not differ from a comparative dose that would be prescribed in the absence of administering the pharmaceutical composition.

X. Certain Indications

In certain embodiments, methods comprise administering a pharmaceutical composition described herein to an animal with a thromboembolic condition. In certain embodiments, methods comprise administering a pharmaceutical composition described herein to an animal at risk for a thromboembolic condition. Thromboembolic conditions include, but are not limited to, thrombosis, embolism, thromboembolism, infarct, deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke, and coronary artery disease (CAD). Risk factors for developing a thromboembolic condition include, a genetic, situational, disease, or environmental factor, or a combination thereof. In certain embodiments, such factors may include, but are not limited to, surgery, cancer, malignancy, pregnancy, older age, use of oral contraceptives, immobility, including travel-related immobility, sepsis, having a mechanical heart valve, valvular heart disease, atrial fibrillation, atherosclerosis atrial fibrillation, genetic predisposition, antiphospholipid syndrome, and inherited or acquired prothrombotic clotting disorders, such as Factor V Leiden. Identifying an animal at risk for developing a thromboembolic condition may be accomplished by any method including evaluating an animal's medical history and standard clinical tests or assessments. In

certain embodiments, the pharmaceutical composition comprises Compound No. 957943. In certain embodiments, the pharmaceutical composition consists or consists essentially of Compound No. 957943 and a pharmaceutically acceptable carrier or diluent.

In certain embodiments, methods comprise administering a pharmaceutical composition described herein to an animal with a disease or condition of the kidney. In certain embodiments, the condition is nephrotoxic drug exposure. In certain embodiments the condition is a genetic or developmental malformation of the kidney, such as that caused by a cystic kidney disease. Non-limiting examples of cystic kidney diseases are autosomal dominant polycystic kidney disease, autosomal recessive polycystic kidney disease, medullary cystic kidney disease and glomerulocystic kidney disease. In certain embodiments, the condition is primary or secondary vesicoureteral reflux. In certain embodiments, the condition is a urethral stricture. In certain embodiments, the condition is a primary or secondary nephrotic syndrome. In certain embodiments, the condition is a primary or secondary glomerulonephritis. In certain embodiments, the condition is lupus nephritis, giant cell arteritis, chronic urinary outflow obstruction, or nephrolithiasis. In certain embodiments, the condition is kidney failure. In certain embodiments, the disease is chronic kidney disease (CKD). In certain embodiments, the disease is end stage renal disease (ESRD). In certain embodiments, the animal is a human subject at risk for CKD or ESRD. Subjects at risk for CKD or ESRD include human subjects who smoke, are obese (*e.g.*, body mass index greater than 30), have hypertension, have diabetes mellitus, receive dialysis, or a combination thereof. In certain embodiments, the human subject is a dialysis patient. The dialysis patient may have previously received dialysis, undergoes dialysis, will receive dialysis, or a combination thereof. In certain embodiments, the human subject is a dialysis patient with ESRD or CKD. Dialysis patients may be at high risk for thrombotic events. Dialysis patients may also be at risk for bleeding events. For example, blood vessels of ESRD patients may be compromised resulting in an increased risk of a thrombotic event or a hemorrhagic event. Thus, dialysis patients may benefit from therapeutic agents that are anti-coagulatory, but do not increase risk of bleeding, such as pharmaceutical compositions described herein. In certain embodiments, the pharmaceutical composition comprises Compound No. 957943. In certain embodiments, the pharmaceutical composition consists or consists essentially of Compound No. 957943 and a pharmaceutically acceptable carrier or diluent.

In certain embodiments, methods comprise administering a pharmaceutical composition described herein to an animal who has been identified as in need of anticoagulation therapy. Examples of such animals include, but are not limited to, those undergoing major orthopedic surgery (*e.g.*, hip/knee replacement or hip fracture surgery) and patients in need of chronic treatment, such as those suffering from arterial fibrillation to prevent stroke. In certain embodiments, methods comprise administering an oligomeric compound described herein, thereby prophylactically reducing a FXI RNA or protein in an animal. Certain embodiments include treating an animal in need thereof by administering to an animal a therapeutically effective amount of a pharmaceutical composition comprising a modified oligonucleotide complementary to a nucleic acid encoding human FXI. In certain embodiments, the pharmaceutical composition comprises Compound No.

957943. In certain embodiments, the pharmaceutical composition consists or consists essentially of Compound No. 957943 and a pharmaceutically acceptable carrier or diluent.

In certain embodiments, methods comprise administering one or more pharmaceutical compositions described herein to an animal who has an inflammatory condition. In certain embodiments, an inflammatory condition means any disease or condition related to an inflammatory response to injury or stimulus characterized by clinical signs of increased redness (rubor), temperature (calor), swelling (tumor), pain (dolor) and/or loss of function (functio laesa) in a tissue. In certain embodiments, examples of such diseases, disorders, and conditions include, but are not limited to, arthritis, colitis, diabetes, sepsis, allergic inflammation, asthma, immunoproliferative disease, antiphospholipid syndrome, graft-related disorder, trauma, autoimmune diseases, vasculitis, or surgery-related disorders. Examples of arthritis include, but are not limited to, rheumatoid arthritis, juvenile rheumatoid arthritis, arthritis uratica, gout, chronic polyarthritis, periarthritis humeroscapularis, cervical arthritis, lumbosacral arthritis, osteoarthritis, psoriatic arthritis, enteropathic arthritis and ankylosing spondylitis. Examples of colitis include, but are not limited to, ulcerative colitis, Inflammatory Bowel Disease (IBD) and Crohn's Disease. Examples of graft-related disorders include, but are not limited to, graft versus host disease (GVHD), disorders associated with graft transplantation rejection, chronic rejection, and tissue or cell allografts or xenografts. Examples of immunoproliferative diseases include, but are not limited to, cancers (*e.g.*, lung cancers) and benign hyperplasias. Examples of autoimmune diseases include, but are not limited to, lupus (*e.g.*, lupus erythematosus, lupus nephritis), Hashimoto's thyroiditis, primary myxedema, Graves' disease, pernicious anemia, autoimmune atrophic gastritis, Addison's disease, diabetes (*e.g.* insulin dependent diabetes mellitus, type I diabetes mellitus, type II diabetes mellitus), good pasture's syndrome, myasthenia gravis, pemphigus, Crohn's disease, sympathetic ophthalmia, autoimmune uveitis, multiple sclerosis, autoimmune hemolytic anemia, idiopathic thrombocytopenia, primary biliary cirrhosis, chronic action hepatitis, ulcerative colitis, Sjogren's syndrome, rheumatic diseases (*e.g.*, rheumatoid arthritis), polymyositis, scleroderma, psoriasis, and mixed connective tissue disease. In certain embodiments, such animal has been identified as at risk for developing an inflammatory condition. In certain embodiments, the animal has a protein C deficiency or a protein S deficiency. In certain embodiments, such animals are at risk of developing an inflammatory condition due to various genetic, situational, disease, or environmental factors. In certain embodiments, such factors may include, but are not limited to, familial history of inflammatory disease such as diabetes, colitis or arthritis, exposure to allergens such as pollen, exposure to material such as asbestos or environmental pollutants. Identifying an animal at risk for developing an inflammatory condition may be accomplished by any method including evaluating the animal's medical history and standard clinical tests or assessments. In certain embodiments, the animal has been identified as in need of anti-inflammatory therapy. Examples of such animals include, but are not limited to, those animals who have been diagnosed with an inflammatory condition and those animals who have a risk factor for developing an inflammatory condition. In certain embodiments, the pharmaceutical composition comprises Compound No. 957943. In certain embodiments,

the pharmaceutical composition consists or consists essentially of Compound No. 957943 and a pharmaceutically acceptable carrier or diluent.

XI. Potency and Efficacy

In certain embodiments, pharmaceutical compositions disclosed herein are sufficiently potent to reduce FXI RNA, FXI protein, FXI activity, or a combination thereof in an animal. In certain embodiments, a single dosage unit of a pharmaceutical composition disclosed herein is sufficiently potent to reduce FXI RNA, FXI protein, FXI activity, or a combination thereof in an animal. In certain embodiments, potency can be determined by determining a first amount of a FXI RNA, FXI protein, or FXI activity before administering a pharmaceutical composition comprising an oligomeric compound disclosed herein and determining a second amount of the FXI RNA, FXI protein, or FXI activity at a relative timepoint after administering, and comparing the first amount to the second amount. In certain embodiments, the relevant timepoint after administering is 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, or 24 hours. In certain embodiments, the relevant timepoint after administering is 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 15 days, 16 days, 17 days, 18 days, 19 days, 20 days, 21 days, 22 days, 23 days, 24 days, 25 days, 26 days, 27 days, 28 days, 29 days, or 30 days. In certain embodiments, the relevant timepoint after administering is greater than 30 days. In certain embodiments, the relevant timepoint after administering is after a final dosage unit of the oligomeric compound is administered to an animal. In certain embodiments, the relevant timepoint is after an intermediate dosage unit of the oligomeric compound is administered to the animal. An amount of reduction in the second amount relative to the first amount may serve as an indication of potency. The amount of reduction may be expressed as percent reduction as demonstrated herein.

In certain embodiments, methods comprise reducing a FXI RNA in an animal. In certain embodiments, methods comprise reducing a FXI protein in an animal. FXI is expressed in the liver but secreted to the blood where it is active. Thus, FXI RNA, FXI protein, and FXI activity levels may be measured in plasma or serum. In certain embodiments, methods disclosed herein reduce a FXI RNA, a FXI protein, and/or a FXI activity. FXI activity may cause a change in blood clotting activity in the animal. The FXI activity may cause a reduction in blood clotting activity in the animal. Blood clotting may be measured by a standard test, for example, but not limited to, activated partial thromboplastin time (aPTT) test, prothrombin time (PT) test, thrombin time (TCT), bleeding time, or presence of D-dimer in a blood sample of the animal. In certain embodiments, a FXI RNA is reduced in a liver or in plasma/serum of an animal by 1-100%, or a range defined by any two of these values. In certain embodiments, a FXI RNA, FXI protein, or FXI activity is reduced by 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%,

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.

957943 may be dosed less frequently than Compound No. 416858. For example, as provided in Example 5, below, in the phase 1 human clinical trial for Compound No. 957943, individuals were administered Compound No. 957943 once every four weeks.

For example, as provided in Example 1 (hereinbelow), Compound No. 957943 demonstrated an ED_{50} for FXI RNA reduction of 0.41 mg/kg in hFXI transgenic mice. Comparator Compound No. 416858 demonstrated an ED_{50} for RNA reduction of 8.35 mg/kg in the same study. Therefore, Compound No. 957943 is demonstrably more potent than comparator Compound No. 416858 in hFXI transgenic mice for RNA reduction.

For example, as provided in Example 1 (hereinbelow), Compound No. 957943 demonstrated greater FXI protein reduction at each dosage level as compared to Compound No. 416858 when Compound No. 957943 was dosed at one-tenth the amount of Compound No. 416858.

For example, as provided in Example 2 (hereinbelow), Compound No. 957943 demonstrated lack of platelet reduction in cynomolgus monkeys. Also, as provided in Example 4 (hereinbelow), Compound No. 957943 demonstrated lack of platelet reduction in human subjects.

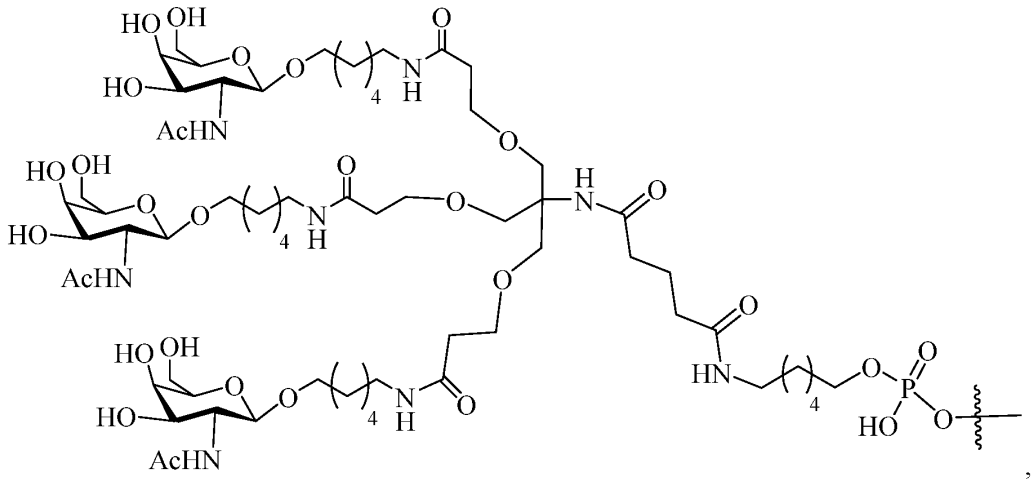
For example, as provided in Example 3 (hereinbelow), Compound No. 957943 demonstrated an EC_{50} for FXI RNA reduction of 0.02 μM with primer probe set RTS2966 and 0.03 μM with primer probe set RTS36807 in HepatoPac® cells. Comparator Compound No. 416858 demonstrated an EC_{50} for FXI RNA reduction of 0.98 μM with primer probe set RTS2966 and 1.07 μM with primer probe set RTS36807 in the same study. Therefore, Compound No. 957943 is demonstrably more potent than comparator Compound No. 416858 in this study.

For example, as provided in Examples 4 and 5 (provided hereinbelow) Compound No. 957943 effectively reduced plasma concentrations of FXI protein and FXI activity in human subjects at all doses and time points tested when administered weekly and monthly.

XIII. Certain Compositions

1. Compound No. 957943

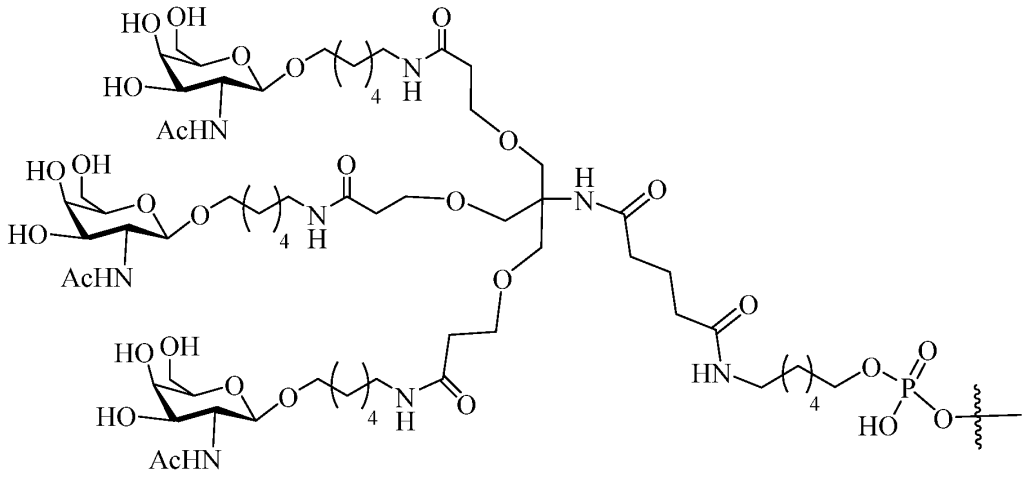
In certain embodiments, Compound No. 957943 is characterized as an oligomeric compound consisting of a conjugate group and a modified oligonucleotide, wherein the conjugate group is a THA-$GalNAc_3$ that is directly attached to the 5' end of the modified oligonucleotide through a phosphodiester linkage, (THA-$GalNAc_3$)o; wherein (THA-$GalNAc_3$)o is represented by the following structure:



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,

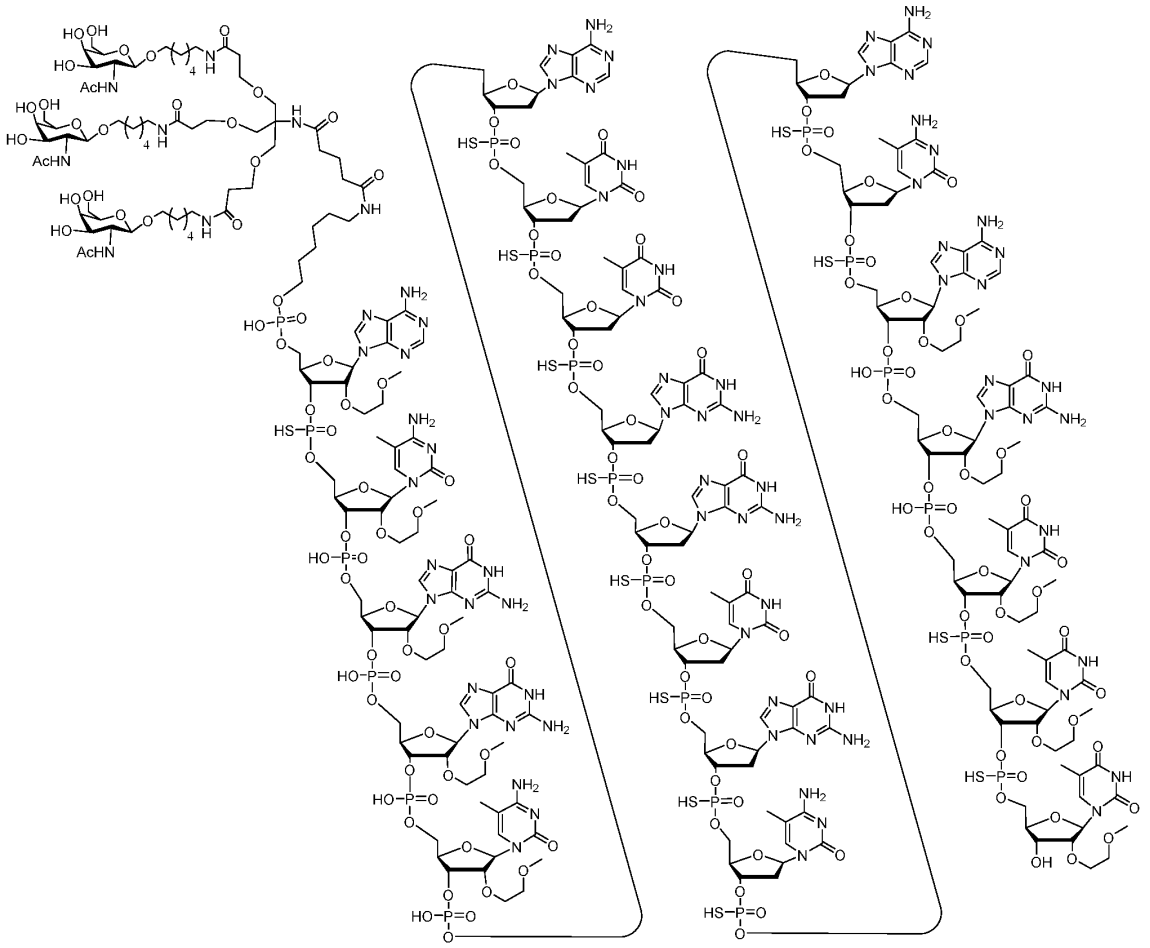
e = a 2'- MOE modified sugar,

d = a 2'-deoxyribose sugar,

s = a phosphorothioate internucleoside linkage, and

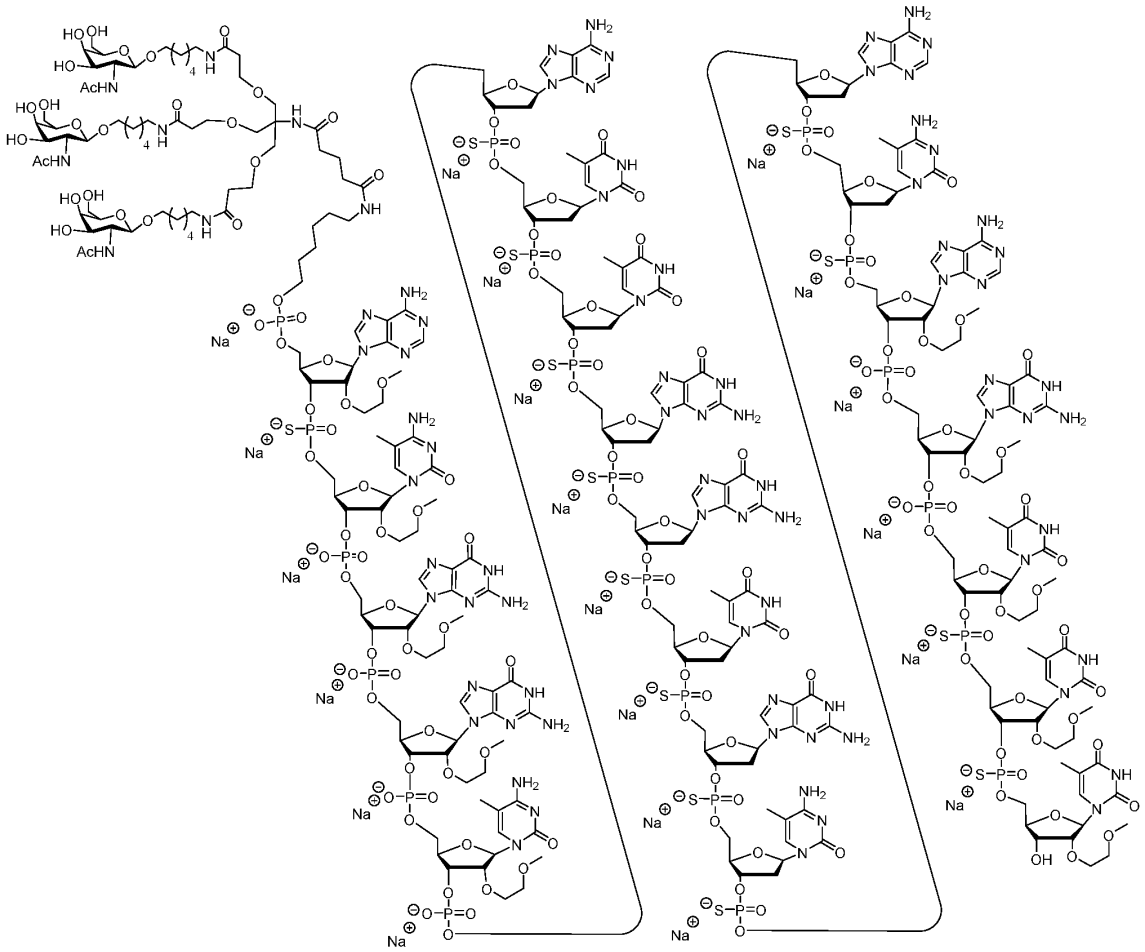
o = a phosphodiester internucleoside linkage.

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



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

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



Structure 2. Sodium salt of Compound No. 957943 (SEQ ID NO: 3)

EXAMPLES

The following examples illustrate certain embodiments of the present disclosure and are not limiting. Moreover, where specific embodiments are provided, the inventors have contemplated generic application of those specific embodiments. For example, disclosure of an oligonucleotide having a particular motif provides reasonable support for additional oligonucleotides having the same or similar motif. And, for example, where a particular high-affinity modification appears at a particular position, other high-affinity modifications at the same position are considered suitable, unless otherwise indicated.

Example 1: Potency of Compound No. 416858 and Compound No. 957943 in transgenic mice

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

an ED_{50} of 0.41 mg/kg. ED_{50} values reported in Table 2 are an average of ED_{50} values that were calculated based on data from a single daily dosing.

Table 2. Percent reduction of human Factor XI RNA in female transgenic mice

Compound No.	Daily Dose (mg/kg/dose)	Liver Factor XI (% control)	ED_{50} (mg/kg)
PBS	-	100	
416858	1.0	80	8.35 mg/kg
	2.5	85	
	5.0	79	
	10.0	40	
	25.0	28	
957943	0.10	74	0.41 mg/kg
	0.25	62	
	0.50	56	
	1.00	27	
	2.50	7	

Protein Analysis

Reduction of FXI plasma protein was demonstrated by ELISA. At the end of the study, blood was collected under anesthesia via cardiac puncture into sample tubes coated with citric acid. Blood was centrifuged at 4000g for 15 minutes and platelet poor plasma was collected and stored at -80 °C prior to analysis. Pooled plasma samples from all groups were analyzed by VisuLize FXI Antigen Kit (Affinity Biologicals INC). Data are presented as the mean of the individual samples.

Table 3. Percent reduction of human Factor XI protein in the plasma of transgenic mice

Compound No.	Dose (mg/kg/dose)	Plasma Factor XI (% control)
PBS	-	100
416858	1.0	81
	2.5	82
	5.0	71
	10.0	56
	25.0	30
957943	0.1	77
	0.25	72
	0.50	59
	1.00	33
	2.50	21

Example 2: Tolerability of oligomeric compounds complementary to human Factor XI in cynomolgus monkeys

Compound No. 416858 was administered to cynomolgus monkeys at 4, 8, 12, and 40 mg/kg/week by subcutaneous injection for 13 weeks, as described in Husam, et. al., "Antisense inhibition of coagulation factor XI prolongs APTT without increased bleeding risk in cynomolgus monkeys", *Blood*, 2012, 119: 2401-2408, incorporated by reference herein in its entirety.

Compound No. 957943 was administered to groups of 14-18 cynomolgus monkeys, half male and half female, at 1, 6, and 25 mg/kg once a month or 1.5 mg/kg weekly by subcutaneous injection. Platelet levels were measured during routine CBC measurements.

Table 4. Platelet Counts in Cynomolgus Monkeys after Treatment with Compound No. 416858, measured at day 93

Dose (weekly)	none (PBS)	4 mg/kg	8 mg/kg	12 mg/kg	40 mg/kg
Platelets (x 10^3/μL)	506	516	452	404	357

Table 5. Platelet Counts in Cynomolgus Monkeys after treatment with Compound No. 957943 for up to 87 days

Dose	none (PBS)	1.5 mg/kg, weekly	1 mg/kg, monthly	6 mg/kg, monthly	25 mg/kg, monthly
Platelets (x 10^3/μL) baseline (9 days pre-treatment)	367	380	355	398	409
Platelets (x 10^3/μL) day 31	378	366	347	372	370
Platelets (x 10^3/μL) day 59	381	386	359	391	396
Platelets (x 10^3/μL) day 87	373	369	352	378	379

Example 3: Potency of Compound No. 416858 and Compound No. 957943 *in vitro* in HepatoPac® cells

The HepatoPac® kit is a commercially-available *in vitro* liver model system available from BIOIVT that consists of micropatterned hepatocyte "islands" co-cultured with supportive stromal cells. A 96-well HepatoPac plate was equilibrated for 48 hours at 37°C and 10% CO_2 in fresh maintenance medium prior to treatment. Oligomeric compounds were diluted into maintenance medium at 0.0002, 0.0020, 0.0200, 0.2000, 2.0000, or 20.0000 μM for 48 hours. After 48 hours, medium was replaced with fresh maintenance medium without additional compound. Cell lysates were collected at 96 hours post compound addition and analyzed by RT-PCR using primer probe set RTS2966 (forward sequence CAGCCTGGAGCATCGTAACA, designated herein as SEQ ID NO: 7; reverse sequence TTTATCGAGCTTCGTTATTCTGGTT designated herein as SEQ ID NO: 8; probe sequence TTGTCTACTGAAGCACACCCAAACAGGGA designated herein

as SEQ ID NO. 9.). IC_{50} was calculated using a linear regression on a log/linear plot of the data in excel. Compound No. 416858 exhibited an IC_{50} of 0.98 μM and Compound No. 957943 exhibited an IC_{50} of 0.02 μM. Data was confirmed using a second primer probe set RTS36807 (forward sequence GCCAGGTAGTCTGCACTTAC, designated herein as SEQ ID NO: 10; reverse sequence GTCCTATTCACTCTTGGCAGT, designated herein as SEQ ID NO. 11; probe sequence CCACCCGATGGTTTACTTGTGTCCT, designated herein as SEQ ID No. 12.). IC_{50} was calculated as described above. Compound No. 416858 exhibited an IC_{50} of 1.07 μM and Compound No. 957943 exhibited an IC_{50} of 0.03 μM.

Table 6. Percent reduction of human Factor XI mRNA in Hepatopac® cells

Compound No.	Dose (μM)	Factor XI (% control) RTS2966	IC_{50} (μM) RTS2966	Factor XI (% control) RTS36807	IC_{50} (μM) RTS36807
PBS	-	100		100	
416858	0.0002	104	0.98	125	1.07
	0.0020	107		110	
	0.0200	102		109	
	0.2000	93		100	
	2.0000	32		28	
	20.0000	8		6	
957943	0.0002	91	0.02	101	0.03
	0.0020	64		56	
	0.0200	62		63	
	0.2000	18		20	
	2.0000	9		7	
	20.0000	11		11	

Example 4: Phase 1 Human Clinical Trial with Compound No. 957943- Single Dose Cohorts

Varying doses of Compound No. 957943 were evaluated in a randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of single doses of Compound No. 957943 in healthy volunteers.

Subjects received doses according to Table 7. Four cohorts of healthy volunteers were enrolled sequentially and randomized to receive Compound No. 957943 or placebo by subcutaneous injection.

Table 7. Single Dose Cohorts

Treatment Assignment	Healthy Volunteers	Doses	Total Dose of Compound No. 957943
Placebo	8	1	0 mg
A	6	1	40 mg
B	6	1	60 mg
C	6	1	80 mg

D	6	1	120 mg

FXI protein concentrations in plasma were measured at baseline, 8 days after treatment, 15 days after treatment, 30 days after treatment and 60 days after treatment. Plasma FXI protein concentrations were measured by a standard ELISA assay. To assay FXI activity, plasma samples from test subjects were added to plasma samples that were immunodepleted of FXI and clotting time for each sample was assayed. Clotting time is proportional to the level of FXI activity in the patient plasma since all other factors are initially present at normal levels. The FXI content of the patient plasma was determined from a reference curve prepared with the FXI deficient plasma and varying dilutions of standard human plasma. The reference value, which was derived from control plasma, was 1.0 unit per milliliter.

Results of the single dose study are presented in **Tables 9-10** and **FIGS. 1A-1B**, and **FIGS. 2A-2B**. **Table 9** and **FIGS. 1A-1B** show results of the activity assay. **Table 10** and **FIGS. 2A-2B** show the results of the ELISA assays.

Table 9. Plasma Factor XI Activity for Single Dose Cohorts

		Baseline	**Day 8**	**Day 15**	**Day 30**	**Day 60**
Placebo (N=8)	Mean	0.999	1.076	1.063	1.034	0.983
	Mean SEM	0.037	0.055	0.055	0.039	0.046
	% change		**8.2**	**6.2**	**3.6**	**0.7**
	% change SEM		5.6	2.9	1.6	3.1
40 mg (N=6)	Mean	1.07	0.718	0.605	0.593	0.702
	Mean SEM	0.042	0.057	0.098	0.103	0.07
	% change		**-33.1**	**-44.8**	**-45.9**	**-34.9**
	% change SEM		3.6	7.5	8.3	5.3
	% change P-value		<0.001	<0.001	<0.001	0.001
60 mg (N=6)	Mean	0.978	0.642	0.487	0.52	0.656
	Mean SEM	0.041	0.057	0.071	0.087	0.074
	% change		**-34.5**	**-50.2**	**-47.2**	**-34.8**
	% change SEM		4.8	6.8	8.2	6
	% change P-value		<0.001	<0.001	<0.001	0.003
80 mg (N=6)	Mean	0.987	0.588	0.446	0.417	0.647
	Mean SEM	0.053	0.067	0.072	0.071	0.087
	% change		**-38.8**	**-54.0**	**-57.8**	**-34.7**
	% change SEM		4.6	5.2	6.5	7.8
	% change P-value		0.002	0.002	<0.001	0.001
120 mg (N=6)	Mean	0.94	0.438	0.227	0.245	0.542
	Mean SEM	0.042	0.029	0.027	0.058	0.084
	% change		**-53.4**	**-75.9**	**-74.4**	**-43.1**
	% change SEM		2.3	2.5	5.5	7.6
	% change P-value		<0.001	<0.001	<0.001	0.001

Input datasets: ADSL and ADEFF.

Note: Baseline is defined as the last non-missing measurement prior to the first dose of study drug.
[A] ANOVA test P-value, [T] Wilcoxon rank sum t approximation test two-sided P-value, [E] Wilcoxon rank sum exact test two-sided P-value.

Table 10. Plasma Factor XI Protein Concentrations for Single Dose Cohorts

		Baseline	Day 8	Day 15	Day 30	Day 60
Placebo (N=8)	Mean	1.19	1.22	1.22	1.22	1.18
	Mean SEM	0.07	0.06	0.08	0.1	0.04
	% change		**3.3**	**3.1**	**3.9**	**3.0**
	% change SEM		4.6	5.8	8.5	6.2
40 mg (N=6)	Mean	1.14	0.68	0.54	0.52	0.81
	Mean SEM	0.03	0.09	0.1	0.09	0.1
	% change		**-41.2**	**-53.8**	**-55.1**	**-29.7**
	% change SEM		6.8	7.6	7.6	8.6
	% change P-value		<0.001	<0.001	<0.001	0.014
60 mg (N=6)	Mean	0.93	0.61	0.45	0.44	0.68
	Mean SEM	0.04	0.07	0.08	0.1	0.08
	% change		**-35.0**	**-52.1**	**-53.5**	**-26.9**
	% change SEM		5.3	7.4	9.5	6.8
	% change P-value		<0.001	<0.001	0.003	0.018
80 mg (N=6)	Mean	1.14	0.56	0.36	0.4	0.69
	Mean SEM	0.08	0.08	0.06	0.08	0.1
	% change		**-49.2**	**-67.0**	**-64.9**	**-38.9**
	% change SEM		5.4	4.6	6.9	9.2
	% change P-value		0.002	0.002	<0.001	0.005
120 mg (N=6)	Mean	1.1	0.44	0.22	0.2	0.54
	Mean SEM	0.05	0.02	0.03	0.05	0.08
	% change		**-59.8**	**-80.0**	**-82.4**	**-51.5**
	% change SEM		2.2	2.1	4.3	6.9
	% change P-value		<0.001	<0.001	<0.001	0.001

Input datasets: ADSL and ADEFF.

Note: Baseline is defined as the last non-missing measurement prior to the first dose of study drug.
[A] ANOVA test P-value, [T] Wilcoxon rank sum t approximation test two-sided P-value, [E] Wilcoxon rank sum exact test two-sided P-value.

Notably, all doses reduced plasma FXI protein concentration and activity by an average of at least 30% at 8 days after receiving the single dose, including the lowest dose of 40 mg. Also, it is noted that plasma FXI protein concentration and activity was reduced by an average of at least 50% at 8 days after receiving the single dose of 120 mg. Plasma FXI protein concentration and activity were further reduced by an average of at least 30% of baseline levels by 15 days after receiving the 120 mg dose. This reduction was maintained at 30 days after dosing. These data suggest that a monthly dosing regimen is sufficient to obtain therapeutic effects of a single dose of Compound No. 957943.

Safety and Tolerability Evaluations

Patient safety was monitored closely during the study. Safety and tolerability evaluations included: physical examination, vital signs (HR, BP, orthostatic changes, weight), ECG, adverse events and concomitant medications, plasma laboratory tests (clinical chemistry, hematology), urinalysis, and complete blood counts (CBC). Platelet levels were measured during routine CBC measurements. Overall, Compound No. 975943 was well-tolerated. There were no safety concerns in vital signs including heart rate and blood pressure, and no clinically relevant changes in liver chemistry, renal function, or platelet values. There were no deaths, no serious adverse events or spontaneous bleeding events.

Example 5: Phase 1 Human Clinical Trial with Compound No. 957943 Multiple Dose Cohorts

Varying doses of Compound No. 957943 were evaluated in a randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple doses of Compound No. 957943 in healthy volunteers. Subjects received doses according to Table 11. Healthy volunteers enrolled in the weekly multiple-dose treatment cohorts (AA, BB, and CC) received six subcutaneous doses of Study Drug (Compound No. 957943 or placebo) starting on Week 1, Day 1 followed by once-weekly subcutaneous administration during Weeks 2 to 6 (Days 8, 15, 22, 29, and 36). Healthy volunteers enrolled in the multiple-dose treatment cohort (DDD) received four subcutaneous doses of Study Drug starting on Week 1, Day 1 followed every four weeks with SC administration during Week 5 (Day 29), Week 9 (Day 57), and Week 13 (Day 85).

Table 11. Multiple Dose Cohorts

Cohort and Dose Level	Healthy Volunteers	Doses	Total Dose of Compound No.957943
AA: 10 mg weekly for 6 weeks (3:1)	8	6	60 mg
BB: 20 mg weekly for 6 weeks (3:1)	8	6	120 mg
CC: 30 mg weekly for 6 weeks (3:1)	8	6	180 mg
DDD: 80 mg every four weeks for 13 weeks (3:2)	10	4	320 mg

Plasma FXI concentrations for cohorts AA, BB and CC were measured by a standard ELISA assay at various time points. Results of the ELISA assay are presented in **Table 12**, **FIG. 3A** and **FIG. 3B**. Plasma FXI activity was also measured (as described in Example 4) at various time points. Results of the activity assay are presented in **Table 13**, **FIG. 4A** and **FIG. 4B**.

Table 12. Plasma Factor XI Activity for Multiple Dose Cohorts AA, BB, CC

		Baseline	**Day 15**	**Day 29**	**Day 43**	**Day 64**	**Day 78**	**Day 92**
Placebo (N=6)	Mean	0.962	0.96	0.91	0.91	0.89	0.856	0.906
	Mean SEM	0.074	0.078	0.06	0.07	0.041	0.07	0.073
	% change		**-0.2**	**-4.6**	**-5.1**	**-6.0**	**-11.4**	**-5.8**
	% change SEM		2.9	3.5	2.2	4.1	5	7.3
	Mean	1.035	0.89	0.635	0.515	0.615	0.637	0.75

10 mg weekly (N=6)	Mean SEM	0.089	0.099	0.095	0.113	0.119	0.101	0.092
	% change		**-13.8**	**-38.2**	**-51.3**	**-41.6**	**-38.1**	**-26.8**
	% change SEM		7.8	9.6	8.6	9.1	10	8.9
	% change P-value		0.093	0.065	0.002	0.009	0.082	0.126
20 mg weekly (N=6)	Mean	0.98	0.775	0.608	0.498	0.494	0.568	0.822
	Mean SEM	0.083	0.091	0.14	0.136	0.082	0.096	0.091
	% change		**-20.6**	**-40.8**	**-51.4**	**-50.8**	**-43.7**	**-17.3**
	% change SEM		7.3	10.2	11.6	7.7	6.8	8.2
	% change P-value		0.065	0.017	0.004	0.004	0.008	0.31
30 mg weekly (N=6)	Mean	0.812	0.448	0.22	0.15	0.215	0.372	0.49
	Mean SEM	0.054	0.036	0.028	0.021	0.03	0.053	0.069
	% change		**-44.6**	**-73.2**	**-81.7**	**-74.1**	**-55.1**	**-41.1**
	% change SEM		2.1	2.6	2.2	2.2	4.7	5.6
	% change P-value		0.004	0.004	0.002	0.002	0.004	0.004

Input datasets: ADSL and ADEFF.

Note: Baseline is defined as the last non-missing measurement prior to the first dose of study drug.

[A] ANOVA test P-value, [T] Wilcoxon rank sum t approximation test two-sided P-value, [E] Wilcoxon rank sum exact test two-sided P-value.

Table 13. Plasma Factor XI Protein Concentrations for Multiple Dose Cohorts AA, BB, CC

		Baseline	**Day 15**	**Day 29**	**Day 43**	**Day 64**	**Day 78**	**Day 92**
Placebo (N=6)	Mean	1.13	1.08	1.08	1.08	1.08	1.01	1.03
	Mean SEM	0.06	0.08	0.08	0.08	0.08	0.05	0.06
	% change		**-4.6**	**-5.1**	**-4.9**	**-4.6**	**-9.1**	**-7.3**
	% change SEM		3.5	3.6	3.4	4.6	3	1.6
10 mg weekly (N=6)	Mean	1.17	0.94	0.74	0.54	0.68	0.78	0.9
	Mean SEM	0.12	0.12	0.13	0.11	0.14	0.14	0.12
	% change		**-20.1**	**-38.5**	**-55.8**	**-44.1**	**-35.0**	**-23.6**
	% change SEM		5.3	5.9	5.8	7.1	7.1	4.2
	% change P-value		0.041	0.002	0.002	0.004	0.017	0.017
20 mg weekly (N=6)	Mean	1.24	0.84	0.64	0.56	0.58	0.72	0.89
	Mean SEM	0.16	0.14	0.2	0.15	0.11	0.11	0.14
	% change		**-31.5**	**-53.0**	**-57.1**	**-55.1**	**-43.9**	**-31.6**
	% change SEM		8.3	10.1	10.6	7.3	6.2	4.6
	% change P-value		0.065	0.004	0.004	0.004	0.008	0.008
30 mg weekly (N=6)	Mean	1.05	0.51	0.23	0.15	0.23	0.39	0.57
	Mean SEM	0.08	0.04	0.04	0.03	0.04	0.06	0.07
	% change		**-51.0**	**-78.7**	**-85.5**	**-78.2**	**-63.0**	**-46.3**
	% change SEM		2.3	2.8	2.3	2.9	4.1	5.3
	% change P-value		0.004	0.004	0.002	0.002	0.004	0.004

Input datasets: ADSL and ADEFF.

Note: Baseline is defined as the last non-missing measurement prior to the first dose of study drug.

[A] ANOVA test P-value, [T] Wilcoxon rank sum t approximation test two-sided P-value, [E] Wilcoxon rank sum exact test two-sided P-value.

Plasma FXI concentrations for cohort DDD were measured by a standard ELISA assay at various time points. Results of the ELISA assay are presented in **Table 14** and **FIG. 5A** and **FIG. 5B**. Plasma FXI activity was measured with an assay conducted in FXI-depleted plasma as described in Example 4 at various time points. FXI activity is presented in **Table 15**, **FIG. 6A** and **FIG. 6B**.

Table 14. Plasma Factor XI Activity for Multiple Dose Cohort DDD

		Baseline	Day 15	Day 29	Day 43	Day 71	Day 99	Day 113
Placebo (N=4)	Mean	0.975	0.958	0.95	0.953	1.03	0.898	0.838
	Mean SEM	0.095	0.153	0.114	0.115	0.118	0.115	0.085
	% change		**-3.0**	**-3.0**	**-2.9**	**-2.1**	**-8.5**	**-14.1**
	% change SEM		7.3	3.2	3.5	3.5	4.4	2
80 mg every 4 weeks (N=6)	Mean	1.145	0.467	0.422	0.238	0.192	0.147	0.198
	Mean SEM	0.073	0.099	0.085	0.048	0.051	0.028	0.039
	% change		**-60.8**	**-63.7**	**-79.6**	**-83.9**	**-87.3**	**-82.8**
	% change SEM		6.4	7.2	3.9	3.9	2.4	3.4
	% change P-value		0.01	0.01	0.01	0.024	0.01	0.01

Input datasets: ADSL and ADEFF.

Note: Baseline is defined as the last non-missing measurement prior to the first dose of study drug.

[A] ANOVA test P-value, [T] Wilcoxon rank sum t approximation test two-sided P-value, [E] Wilcoxon rank sum exact test two-sided P-value.

Table 15. Plasma Factor XI Protein Concentrations for Multiple Dose Cohort DDD

		Baseline	Day 15	Day 29	Day 43	Day 71	Day 99	Day 113
Placebo (N=4)	Mean	1.09	1.17	1.02	1.06	1.15	1.1	1.01
	Mean SEM	0.18	0.12	0.14	0.14	0.16	0.16	0.12
	% change		**12.0**	**-3.9**	**-0.7**	**-5.6**	**3.2**	**-4.4**
	% change SEM		11.3	7.7	3.8	3.1	6.6	6
80 mg every 4 weeks (N=6)	Mean	1.33	0.51	0.45	0.26	0.23	0.19	0.25
	Mean SEM	0.15	0.13	0.1	0.06	0.08	0.05	0.05
	% change		**-63.8**	**-66.1**	**-81.1**	**-83.9**	**-85.5**	**-80.6**
	% change SEM		6.9	7	3.7	4.5	3.1	3.9
	% change P-value		0.01	0.01	0.01	0.024	0.01	0.01

Input datasets: ADSL and ADEFF.

Note: Baseline is defined as the last non-missing measurement prior to the first dose of study drug.

[A] ANOVA test P-value, [T] Wilcoxon rank sum t approximation test two-sided P-value, [E] Wilcoxon rank sum exact test two-sided P-value.

FXI plasma protein and activity was reduced in all subjects receiving Compound No. 957943 at all doses at all time points. Results of these studies support a monthly dosing regimen.

Safety and Tolerability Evaluations

Patient safety was monitored closely during the study. Safety and tolerability evaluations included: physical examination, vital signs (HR, BP, orthostatic changes, weight), ECG, adverse events and concomitant medications, plasma laboratory tests (clinical chemistry, hematology), urinalysis, and complete blood counts (CBC). Platelet levels were measured during routine CBC measurements. Overall, Compound No. 975943 was well-tolerated. There were no safety concerns in vital signs including heart rate and blood pressure, and no clinically relevant changes in liver chemistry, renal function, or platelet values. No deaths, spontaneous bleeding, or serious adverse events were observed.

Example 6: Phase 2 Human Clinical Trial with Compound No. 957943

Multiple doses of Compound No. 957943 are evaluated in a Phase 2 multicenter, randomized, placebo-controlled study in ESRD patients receiving hemodialysis. Patients are randomized to receive subcutaneous treatment (low, mid, high dose) with either Compound No. 957943 or placebo. All standard of care hemodialysis therapies as prescribed by their providers are continued, except anticoagulants or antiplatelet medications other than acetylsalicylic acid (*e.g.*, aspirin) up to 150 mg daily.

All cohorts consist of a screening and approximately 6 months treatment period followed by a post-treatment follow-up period.

Pharmacodynamics and efficacy are assessed at multiple time points. Patient safety is monitored closely during the study. Safety and tolerability evaluations may include *e.g.* physical examination, vital signs, adverse events, concomitant medications, and plasma laboratory tests.