(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
03 November 2022 (03.11.2022)

WIPO | PCT

(10) International Publication Number
WO 2022/232650 A1

(51) International Patent Classification:
A61K 48/00 (2006.01) *A61K 31/712* (2006.01)
C07H 21/02 (2006.01)

(21) International Application Number:
PCT/US2022/027138

(22) International Filing Date:
29 April 2022 (29.04.2022)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/182,518 30 April 2021 (30.04.2021) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:
— *with international search report (Art. 21(3))*
— *with sequence listing part of description (Rule 5.2(a))*

(54) Title: METHODS FOR REDUCING AGT EXPRESSION

(57) Abstract: Provided herein are methods of administering ISIS 757456 for treating hypertension (HTN); resistant hypertension (RHTN); heart failure; chronic heart failure; heart failure with reduced ejection fraction (HFrEF); heart failure with preserved ejection fraction (HFpEF); diabetic nephropathy (DN); aortopathies associated with pathogenic TGF-β signaling including Marfan Syndrome, Loeys-Dietz Syndrome, Hereditary Hemorrhagic Telangiectasia, and Familial Thoracic Aortic Aneurysm and Dissection; chronic kidney disease; hepatic steatosis; or atherosclerosis. Also provide herein are methods of reducing AGT RNA or protein in a human subject in need thereof.

WO 2022/232650 A1

METHODS FOR REDUCING AGT 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 BIOL0412WOSEQ_ST25.txt, created on April 25, 2022, which is 25 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 methods of administering ISIS 757456 for treating hypertension (HTN); resistant hypertension (RHTN); heart failure; chronic heart failure; heart failure with reduced ejection fraction (HFrEF); heart failure with preserved ejection fraction (HFpEF); diabetic nephropathy (DN); aortopathies associated with pathogenic TGF-β signaling including, e.g., Marfan Syndrome, Loeys-Dietz Syndrome, Hereditary Hemorrhagic Telangiectasia, and Familial Thoracic Aortic Aneurysm and Dissection; chronic kidney disease; hepatic steatosis; or atherosclerosis in a human subject. Also provided herein are methods of administering ISIS 757456 for reducing angiotensinogen (AGT) RNA or protein in a human subject in need thereof.

Background

The renin-angiotensin-aldosterone system (RAAS) is an integral neuro-hormonal mechanism involved in the regulation of vascular tone and fluid homeostasis. The systemic RAAS cascade begins with renin-mediated cleavage of angiotensinogen (AGT), whose plasma levels are primarily liver derived, to generate angiotensin I. Angiotensin converting enzyme converts angiotensin I to angiotensin II (Ang II), a potent vasoactive peptide involved in vasoconstriction and aldosterone release. The RAAS acts as a key regulator of acute hemodynamic changes, but persistent activation results in excessive vasoconstriction, salt and water retention, cardiac hypertrophy, and fibrosis. Chronic overactivity of the RAAS pathway is considered a major contributor to the pathogenesis of cardiovascular disorders, including hypertension, chronic kidney disease and heart failure.

Heart failure (HF) is a global public health issue characterized by significant mortality, frequent hospitalization, and poor QOL, with an overall prevalence that is steadily increasing across the globe. Heart failure afflicts approximately 6.5 million patients in the United States and 26 million worldwide (Savarese and Lund, *Cardiac Failure Review* 2017; 3: 7-11). As the population ages, heart failure incidence is increasing, and >550,000 patients are diagnosed with new heart failure each year. Heart Failure is responsible for more hospitalizations than all forms of cancer combined and is the most common diagnosis in hospital patients age 65 years and older. Every year over 1 million patients are hospitalized for heart failure in the US and Europe, accounting for 6.5 million hospital days (Ambrosy et al., *Curr Heart Fail Rep* 2014; 11: 416-427). High rates of hospitalizations with frequent readmission (almost 25% of patients with HF are readmitted within 30 days) along with other direct and indirect costs, also place an enormous economic burden on healthcare systems

Summary

Provided herein are methods for treating hypertension (HTN); resistant hypertension (RHTN); heart failure; chronic heart failure; heart failure with reduced ejection fraction (HFrEF); heart failure with preserved ejection fraction (HFpEF); diabetic nephropathy (DN); aortopathies associated with pathogenic TGF-β signaling including, e.g., Marfan Syndrome, Loeys-Dietz Syndrome, Hereditary Hemorrhagic Telangiectasia, and Familial Thoracic Aortic Aneurysm and Dissection; chronic kidney disease; hepatic steatosis; or atherosclerosis in a human subject. Also provided herein are methods of reducing angiotensinogen (AGT) RNA or protein in a human subject having hypertension (HTN); resistant hypertension (RHTN); heart failure; chronic heart failure; heart failure with reduced ejection fraction (HFrEF); heart failure with preserved ejection fraction (HFpEF); diabetic nephropathy (DN); aortopathies associated with pathogenic TGF-β signaling including, e.g., Marfan Syndrome, Loeys-Dietz Syndrome, Hereditary Hemorrhagic Telangiectasia, and Familial Thoracic Aortic Aneurysm and Dissection; chronic kidney disease; hepatic steatosis; or atherosclerosis.

Heart failure with reduced ejection fraction (HFrEF) is a complex clinical syndrome characterized by the heart's reduced capacity to pump blood (Yancy et al., *Am Coll Cardiol* 2013; 62: e147-239). Signs and symptoms of heart failure include those due to fluid volume excess (dyspnea, orthopnea, edema, hepatic congestion, ascites) and those due to a diminished cardiac output (fatigue, dizziness, weakness). Fluid retention in heart failure is initiated by the fall in cardiac output, leading to alterations in renal function, and subsequent compensatory activation of the sodium-retaining renin-angiotensinaldosterone system (RAAS) and sympathetic nervous systems. The net effect of these neurohumoral responses is to produce hemodynamic changes in heart, kidneys and vasculature to increase blood volume and then ventricular filling. However, chronic activation of neurohormonal response results in hemodynamic stress and progression of HF.

HF with preserved EF (HFpEF) is characterized by a normal cardiac output but abnormal diastolic function, often with left ventricular (LV) concentric remodeling or hypertrophy. Currently, no clinical trials have shown benefits in the subset of subjects with HFpEF, which represents approximately 50% of HF cases. Comorbidities such as hypertension, diabetes mellitus, and CKDs are highly prevalent and are implicated in development and progression of HFpEF. Thus, it seems reasonable that RAAS suppression may benefit HFpEF as well.

Hypertension (HTN) is characterized as failure to achieve blood pressure (BP) goal < 140/90 mmHg. HTN is a major contributor to cardiovascular disease (CVD) morbidity and mortality and chronic kidney disease. Approximately 1.5 M people in the US have myocardial infarction or stroke annually, with ~50% of these major adverse cardiovascular events attributed to HTN (Lawes et al., *Lancet* 2008; 371: 1513-1518; Korsnes et al., *J Manag Care Spec Pharm* 2015; 21: 443-450). Inadequate BP control can lead to increase cardiovascular risk. Some patients have pseudo-resistance HTN as they are not compliant with their

medications or they have white coat HTN. Lowering blood pressure reduces cardiovascular (CV) risk including major CV events, chronic heart disease (CHD), stroke, heart failure, renal failure, all-cause mortality (Ettehad et al., *The Lancet* 2016; 387: 957-967). Providing sustained and controlled blood pressure with weekly or less administration could benefit patients inadequately controlled with daily administered therapies. Night-time systolic blood pressure (SBP) has consistently been shown to be an important predictor of CV risk. A 10 mmHg increase in night-time SBP can increase risk of total CV events, stroke and cardiac mortality in diabetic patients (Draman et al., *J Hypertens* 2015; 33: 1373-1377).

Resistant hypertension (RHTN) is characterized as failure to achieve blood pressure (BP) goal in patients on 3 or more antihypertensive medications, which typically belong to one or more of the following classes of medications: a diuretic, a long-acting calcium channel blocker, a beta blocker, or a renin-angiotensin pathway blocker such as an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker. (Carey RM et al., *Hypertension* 2018 Nov; 72(5):e53-e90; Judd and Calhoun, *J Hum Hypertens* 2014; 28: 463-468; Sigmund et al., *Hypertension* 2020; 75: 902-917). In US alone, 70 million adults have HTN, of which 12-15% have RHTN. Among these patients 33% of them have uncontrolled RHTN (Judd and Calhoun 2014). In an analysis of National Health and Nutrition Examination Survey database, these patients are more likely to be black, with diabetes, with chronic kidney disease (CKD) Stage 3, with proteinuria and congestive heart failure compared to patients with HTN and without resistant HTN.

In certain embodiments, methods comprise administering a therapeutically effective amount of a modified oligonucleotide. In certain embodiments, the modified oligonucleotide is ISIS 757456. In certain embodiments, the therapeutically effective amount is within the range of about 5 mg to about 200 mg of ISIS 757456. In certain embodiments, the therapeutically effective amount is or is about 5 mg, about 10 mg, about 20 mg, about 40 mg, about 60 mg, about 80 mg, about 100 mg, or about 120 mg of ISIS 757456. In certain embodiments, the therapeutically effective amount is or is about 80 mg of ISIS 757456. In certain embodiments, the therapeutically effective amount is or is about 120 mg of ISIS 757456. In certain embodiments, the therapeutically effective amount is administered once every day. In certain embodiments, the therapeutically effective amount is administered once every other day. In certain embodiments, the therapeutically effective amount is administered once every 3 days. In certain embodiments, the therapeutically effective amount is administered once every 4 days. In certain embodiments, the therapeutically effective amount is administered once every 5 days. In certain embodiments, the therapeutically effective amount is administered once every 6 days. In certain embodiments, the therapeutically effective amount is administered once every week. In certain embodiments, the therapeutically effective amount is administered once every 2 weeks. In certain embodiments, the therapeutically effective amount is administered once every 3 weeks. In certain embodiments, the therapeutically effective amount is administered once every 4 weeks. In certain embodiments, the therapeutically effective amount is administered twice every week. In certain embodiments, the therapeutically effective amount is administered three times every week. In certain embodiments, the therapeutically effective amount is administered four times every week. In certain embodiments, the

therapeutically effective amount is administered five times every week. In certain embodiments, the therapeutically effective amount is administered six times every week. In any of the foregoing embodiments, ISIS 757456 can be administered by a syringe.

Detailed Description

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:

As used herein, "2'-deoxyribonucleoside" means a nucleoside comprising a 2'-H(H) deoxyribosyl sugar moiety. In certain embodiments, a 2'-deoxyribonucleoside is a 2'-β-D deoxyribonucleoside and comprises a 2'-β-D-deoxyribosyl sugar moiety, which has the β-D configuration as found in naturally occurring deoxyribonucleic acids (DNA). In certain embodiments, a 2'-deoxyribonucleoside may comprise a modified nucleobase or may comprise an RNA nucleobase (uracil).

As used herein, "2'-MOE" means a 2'-$OCH_2CH_2OCH_3$ group in place of the 2'-OH group of a ribosyl sugar moiety. A "2'-MOE sugar moiety" is a sugar moiety with a 2'-$OCH_2CH_2OCH_3$ group in place of the 2'-OH group of a ribosyl sugar moiety. Unless otherwise indicated, a 2'-MOE sugar moiety is in the β-D configuration. "MOE" means O-methoxyethyl.

As used herein, "2'-MOE nucleoside" means a nucleoside comprising a 2'-MOE sugar moiety.

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 a human subject.

As used herein, "dose" means a quantity of a pharmaceutical agent administered.

As used herein, "AGT RNA" is the RNA expression product of the human gene, *angiotensinogen*.

As used herein, "AGT protein" is the protein expression product of AGT RNA.

As used herein, the term "internucleoside linkage" means the covalent linkage between contiguous 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, "loading dose" means a therapeutically effective amount of a pharmaceutical agent administered during an initial dosing phase during which steady state concentration of the pharmaceutical agent is achieved. "Initial loading dose" means the first loading dose administered. "Last loading dose" means the loading dose administered most recently prior to administering a first maintenance dose.

As used herein, "maintenance dose" means a therapeutically effective amount of a pharmaceutical agent administered during a dosing phase after steady state concentration of the pharmaceutical agent has been achieved.

As used herein, "nucleobase" means an unmodified nucleobase or modified nucleobase. An "unmodified nucleobase" is adenine (A), thymine (T), cytosine (C), uracil (U), or guanine (G). A "modified nucleobase" is 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. As used herein, "nucleobase sequence" means the order of contiguous nucleobases in a target 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. "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, "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, "pharmaceutically acceptable carrier or diluent" means any substance suitable for use in administering to a human subject. 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 a human subject. In certain embodiments, a pharmaceutically acceptable carrier or diluent is sterile water, sterile saline, or sterile buffer solution.

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, "potassium salt" means a salt of a modified oligonucleotide, wherein the cation of the salt is potassium.

As used herein, "RNA" means an RNA transcript and includes pre-mRNA and mature mRNA unless otherwise specified.

As used herein, "sodium salt" means a salt of a modified oligonucleotide, wherein the cation of the salt is sodium.

As used herein, "subject" means a human or non-human animal. In certain embodiments, the subject is a human subject. A "subject in need thereof," is a subject who would benefit from administration of a modified oligonucleotide disclosed herein. In certain embodiments, the subject in need thereof has hypertension (HTN); resistant hypertension (RHTN); heart failure; chronic heart failure; heart failure with reduced ejection fraction (HFrEF); heart failure with preserved ejection fraction (HFpEF); diabetic nephropathy (DN); aortopathies associated with pathogenic TGF-β signaling including, e.g., Marfan Syndrome, Loeys-Dietz Syndrome, Hereditary Hemorrhagic Telangiectasia, and Familial Thoracic Aortic Aneurysm and Dissection; chronic kidney disease; hepatic steatosis; or atherosclerosis.

As used herein, "sugar moiety" means an unmodified sugar moiety or a modified sugar moiety. "Unmodified sugar moiety" means a 2'-OH(H) β-D ribosyl moiety, as found in RNA (an "unmodified RNA sugar moiety"), or a 2'-H(H) β-D 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. "Modified sugar moiety" or "modified sugar" means a modified furanosyl sugar moiety or a sugar surrogate.

As used herein, "symptom" means any physical feature or test result that indicates the existence or extent of a disease or disorder. In certain embodiments, a symptom is apparent to a subject or to a medical professional examining or testing the subject.

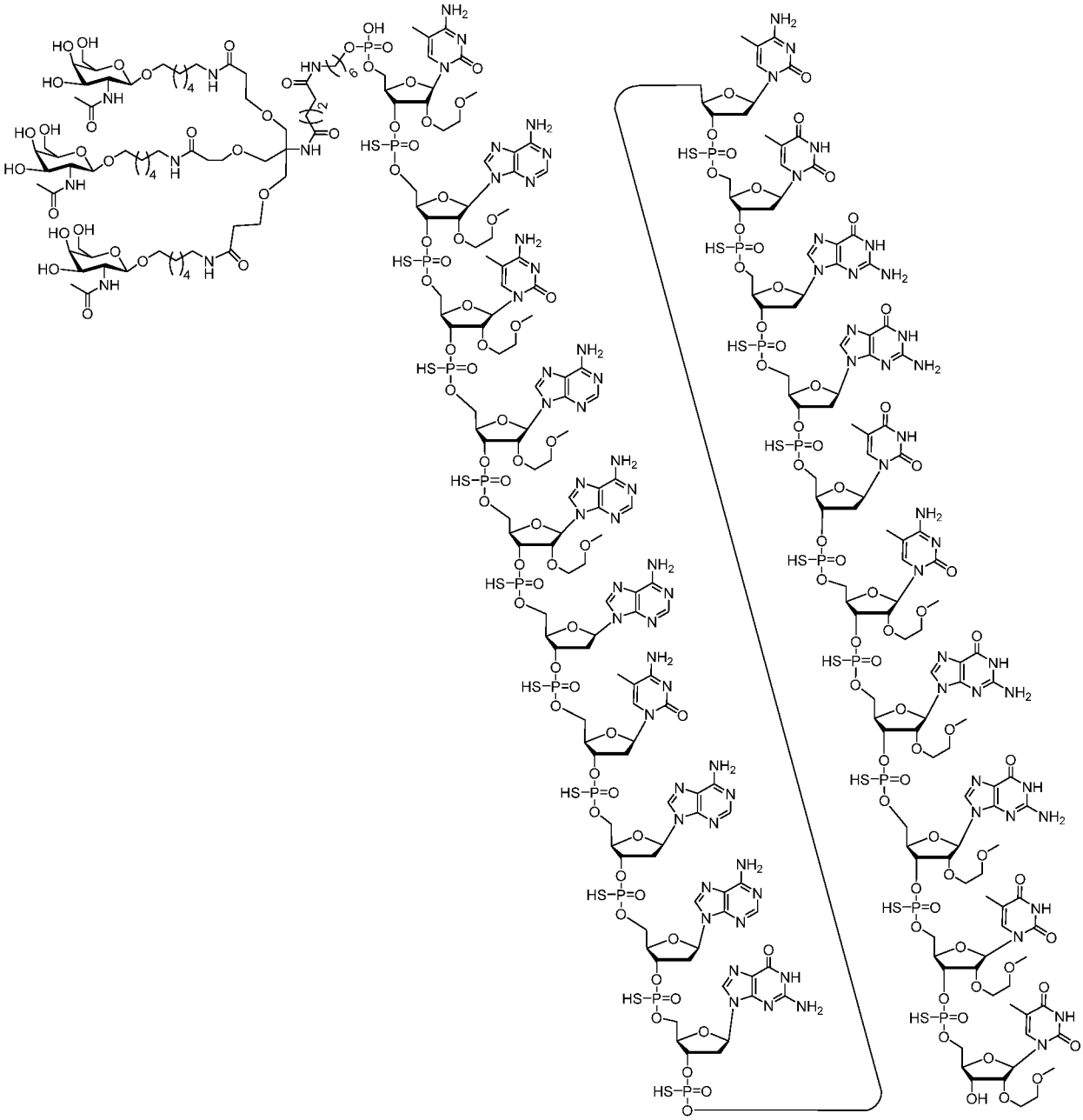
As used herein, "treating" refers to administering a compound or pharmaceutical composition to a subject in order to effect an alteration or improvement of a disease, disorder, or condition in the subject. In certain embodiments, treating includes amelioration.

As used herein, "therapeutically effective amount" means an amount of a pharmaceutical agent that provides a therapeutic benefit to a human subject. For example, a therapeutically effective amount improves a symptom of a disease.

As used herein, "week" means 7 days.

CERTAIN EMBODIMENTS

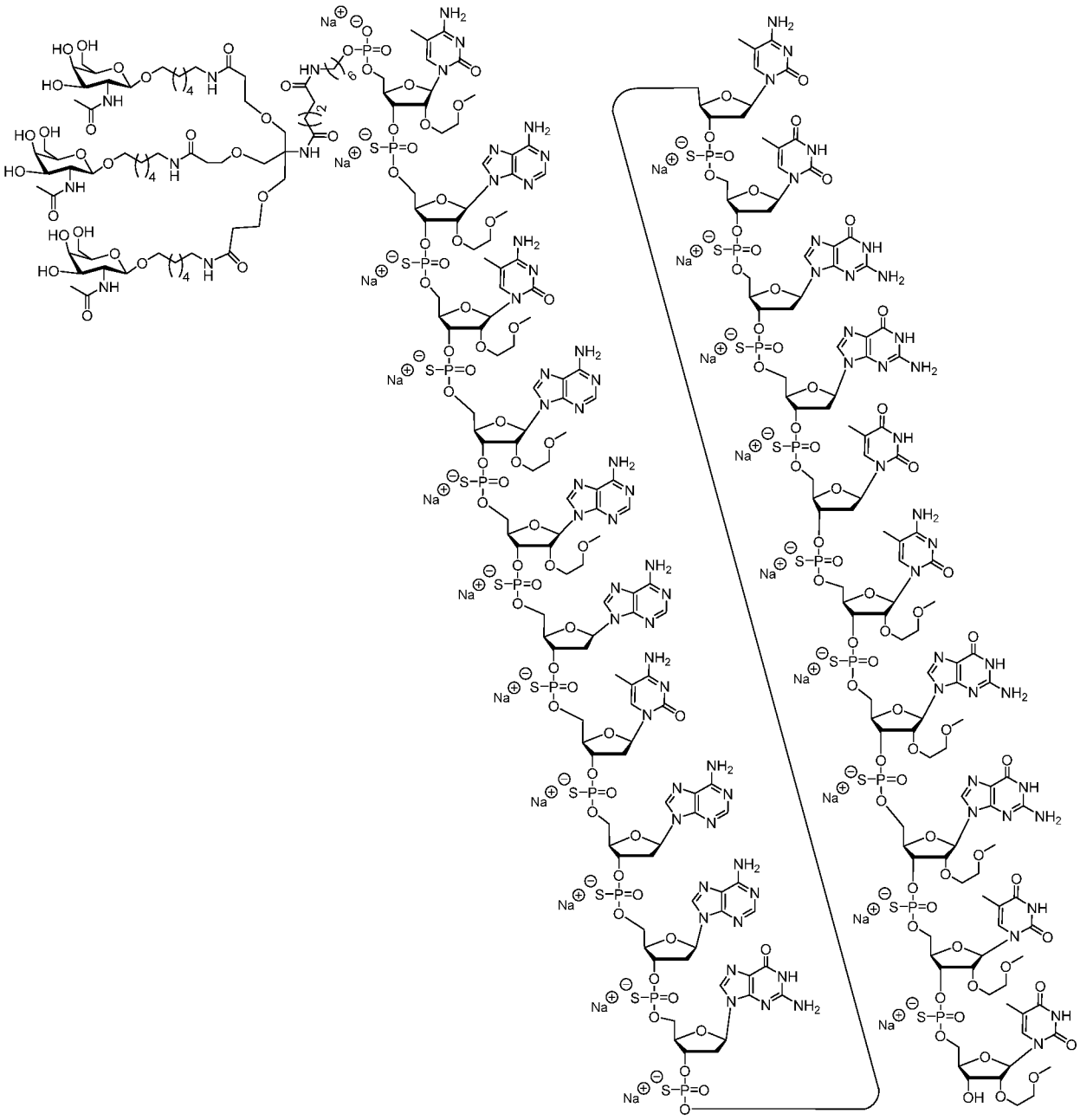
Embodiment 1. A method of treating hypertension (HTN); resistant hypertension (RHTN); heart failure; chronic heart failure; heart failure with reduced ejection fraction (HFrEF); heart failure with preserved ejection fraction (HFpEF); diabetic nephropathy (DN); aortopathies associated with pathogenic TGF-β signaling; Marfan Syndrome; Loeys-Dietz Syndrome; Hereditary Hemorrhagic Telangiectasia; Familial Thoracic Aortic Aneurysm and Dissection; chronic kidney disease; hepatic steatosis; or atherosclerosis in a human subject comprising administering to the human subject a therapeutically effective amount of an oligomeric compound according to the following chemical structure:



(SEQ ID NO: 3), or a salt thereof.

Embodiment 2. The method of embodiment 1, wherein the oligomeric compound is the sodium salt or the potassium salt.

Embodiment 3. A method of treating hypertension (HTN); resistant hypertension (RHTN); heart failure; chronic heart failure; heart failure with reduced ejection fraction (HFrEF); heart failure with preserved ejection fraction (HFpEF); diabetic nephropathy (DN); aortopathies associated with pathogenic TGF-β signaling; Marfan Syndrome; Loeys-Dietz Syndrome; Hereditary Hemorrhagic Telangiectasia; Familial Thoracic Aortic Aneurysm and Dissection; chronic kidney disease; hepatic steatosis; or atherosclerosis in a human subject comprising administering to the human subject a therapeutically effective amount of an oligomeric compound according to the following chemical structure:



(SEQ ID NO: 3).

Embodiment 4. A method of treating hypertension (HTN); resistant hypertension (RHTN); heart failure; chronic heart failure; heart failure with reduced ejection fraction (HFrEF); heart failure with preserved ejection fraction (HFpEF); diabetic nephropathy (DN); aortopathies associated with pathogenic TGF-β signaling; Marfan Syndrome; Loeys-Dietz Syndrome; Hereditary Hemorrhagic Telangiectasia; Familial Thoracic Aortic Aneurysm and Dissection; chronic kidney disease; hepatic steatosis; or atherosclerosisin a human subject comprising administering to the human subject a therapeutically effective amount of an oligomeric compound comprising a modified oligonucleotide and a conjugate group according to the following formula: $GalNAc_3$-$7_{a\text{-}o'}$ mCes Aes mCes Aes Aes Ads mCds Ads Ads Gds mCds Tds Gds Gds Tds mCes Ges Ges Tes Te (SEQ ID NO: 3); wherein,

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

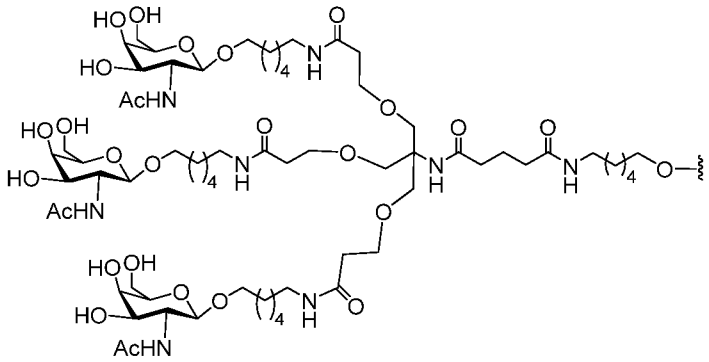
e = a 2'-MOE sugar moiety,

d = a 2'-β-D-deoxyribosyl sugar moiety,

s = a phosphorothioate internucleoside linkage,

o' = 5'-P(OH)(=O)-O-3', and

$GalNAc_3$-7_a =



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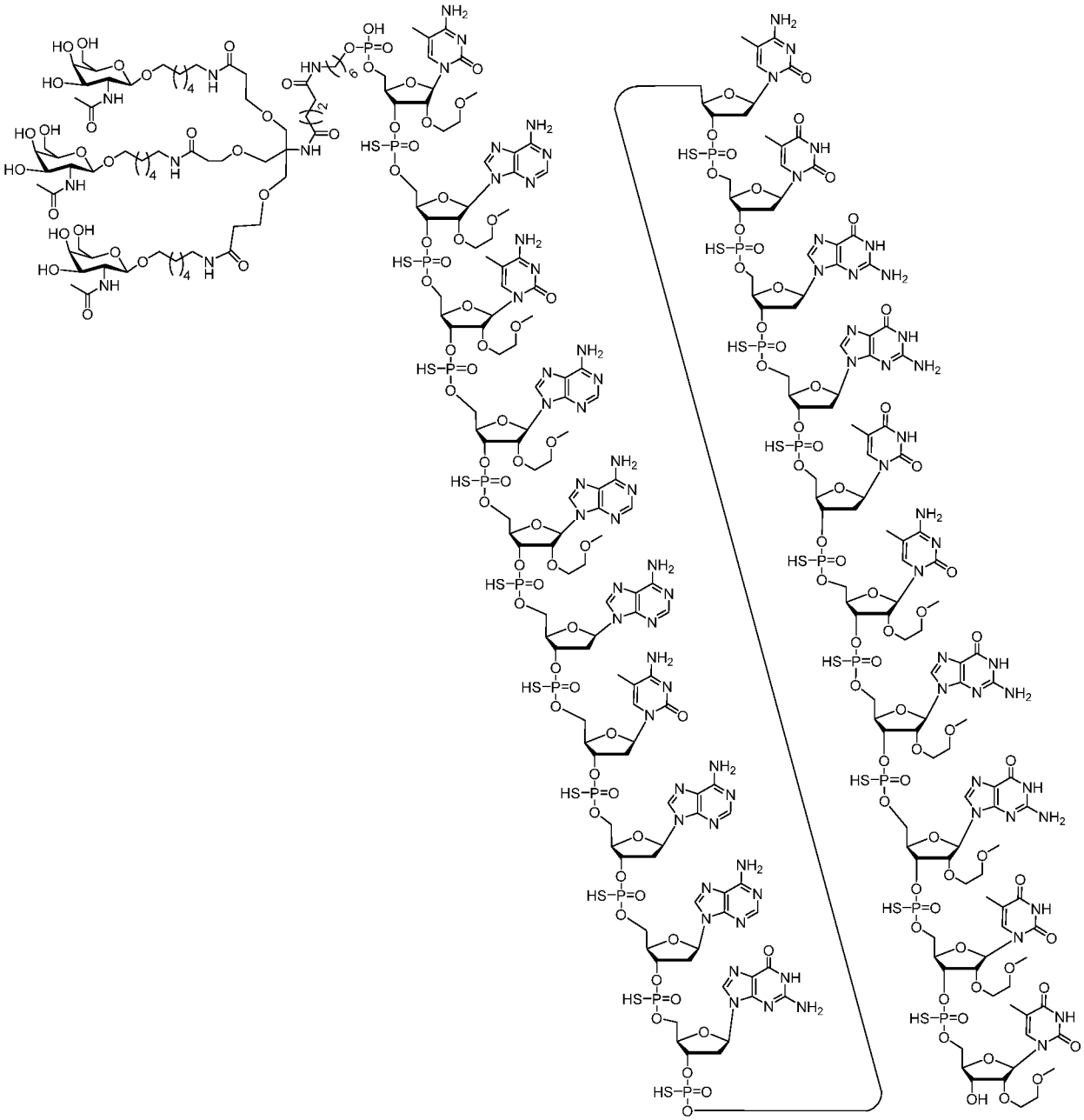
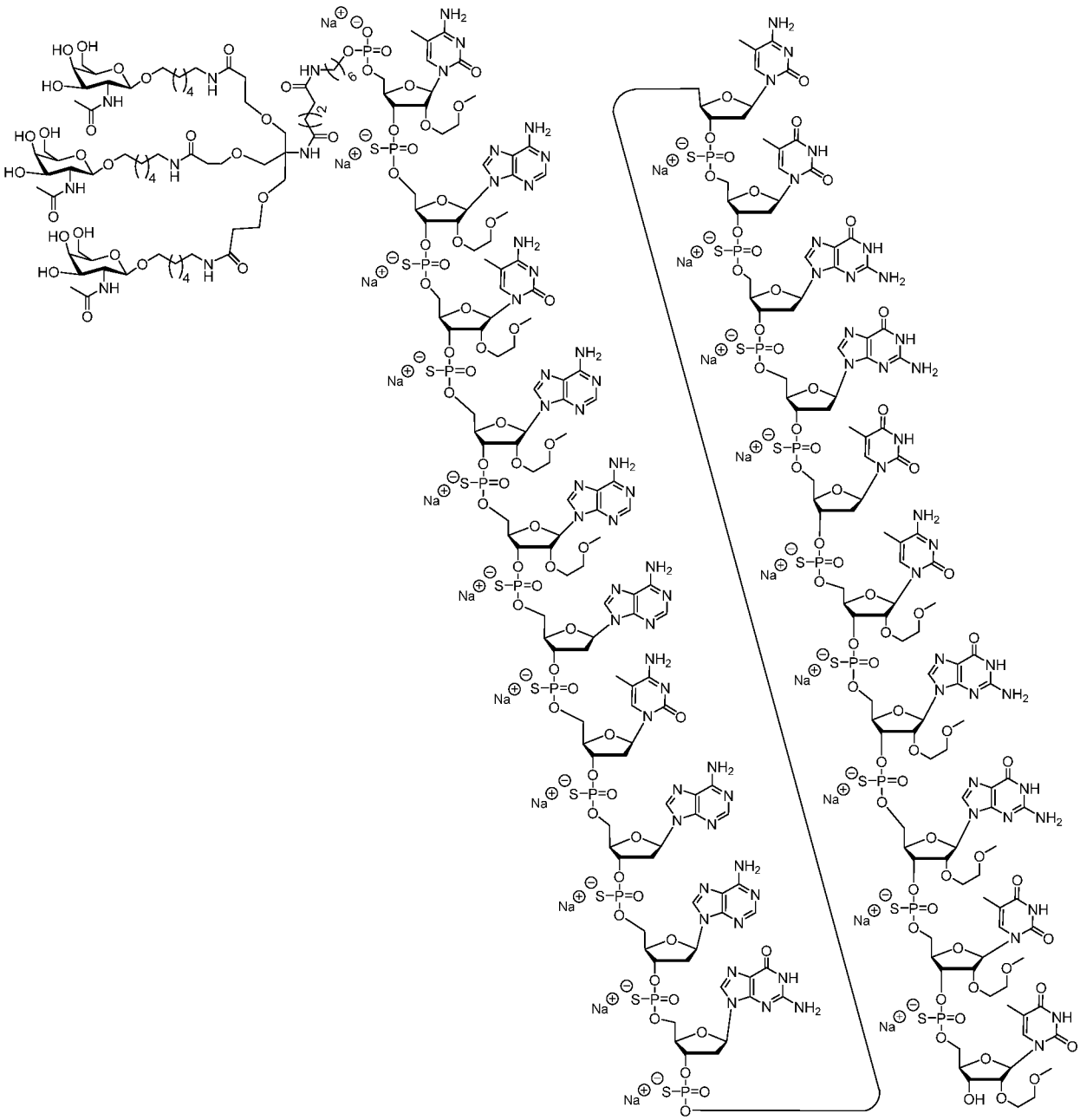
Embodiment 5. A method of reducing AGT RNA or protein in a human subject having hypertension (HTN); resistant hypertension (RHTN); heart failure; chronic heart failure; heart failure with reduced ejection fraction (HFrEF); heart failure with preserved ejection fraction (HFpEF); diabetic nephropathy (DN); aortopathies associated with pathogenic TGF-β signaling; Marfan Syndrome; Loeys-Dietz Syndrome; Hereditary Hemorrhagic Telangiectasia; Familial Thoracic Aortic Aneurysm and Dissection; chronic kidney disease; hepatic steatosis; or atherosclerosis comprising administering to the human subject a therapeutically effective amount of an oligomeric compound according to the following chemical structure:



(SEQ ID NO: 3), or a salt thereof.

Embodiment 6. The method of embodiment 5, wherein the oligomeric compound is the sodium salt or the potassium salt.

Embodiment 7. A method of reducing AGT RNA or protein in a human subject having hypertension (HTN); resistant hypertension (RHTN); heart failure; chronic heart failure; heart failure with reduced ejection fraction (HFrEF); heart failure with preserved ejection fraction (HFpEF); diabetic nephropathy (DN); aortopathies associated with pathogenic TGF-β signaling; Marfan Syndrome; Loeys-Dietz Syndrome; Hereditary Hemorrhagic Telangiectasia; Familial Thoracic Aortic Aneurysm and Dissection; chronic kidney disease; hepatic steatosis; or atherosclerosis comprising administering to the human subject a therapeutically effective amount of an oligomeric compound according to the following chemical structure:



(SEQ ID NO: 3).

Embodiment 8. A method of reducing AGT RNA or protein in a human subject having hypertension (HTN); resistant hypertension (RHTN); heart failure; chronic heart failure; heart failure with reduced ejection fraction (HFrEF); heart failure with preserved ejection fraction (HFpEF); diabetic nephropathy (DN); aortopathies associated with pathogenic TGF-β signaling; Marfan Syndrome; Loeys-Dietz Syndrome; Hereditary Hemorrhagic Telangiectasia; Familial Thoracic Aortic Aneurysm and Dissection; chronic kidney disease; hepatic steatosis; or atherosclerosis comprising administering to the human subject a therapeutically effective amount of an oligomeric compound comprising a modified oligonucleotide and a conjugate group according to the following formula: $GalNAc_3$-7_{a-o}, mCes Aes mCes Aes Aes Ads mCds Ads Ads Gds mCds Tds Gds Gds Tds mCes Ges Ges Tes Te (SEQ ID NO: 3); wherein,

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

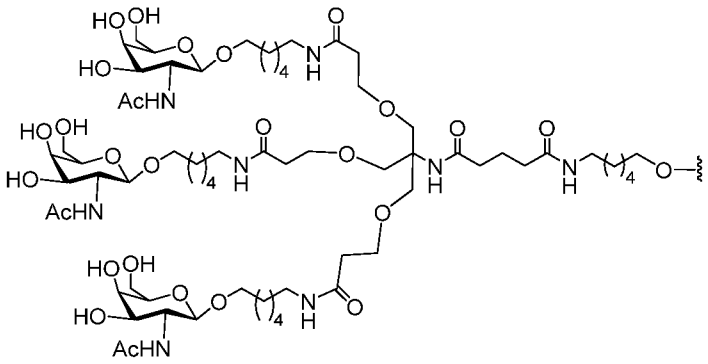
e = a 2'-MOE sugar moiety,

d = a 2'-β-D-deoxyribosyl sugar moiety,

s = a phosphorothioate internucleoside linkage,

o' = 5'-P(OH)(=O)-O-3', and

GalNAc$_3$-7$_a$ =



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Embodiment 9. The method of any one of embodiments 1-8, wherein the therapeutically effective amount is 25 mg.

Embodiment 10. The method of any one of embodiments 1-8, wherein the therapeutically effective amount is 40 mg.

Embodiment 11. The method of any one of embodiments 1-8, wherein the therapeutically effective amount is 60 mg.

Embodiment 12. The method of any one of embodiments 1-8, wherein the therapeutically effective amount is 80 mg.

Embodiment 13. The method of any one of embodiments 1-8, wherein the therapeutically effective amount is 120 mg.

Embodiment 14. The method of any one of embodiments 1-8, wherein the therapeutically effective amount is about 25 mg.

Embodiment 15. The method of any one of embodiments 1-8, wherein the therapeutically effective amount is about 40 mg.

Embodiment 16. The method of any one of embodiments 1-8, wherein the therapeutically effective amount is about 60 mg.

Embodiment 17. The method of any one of embodiments 1-8, wherein the therapeutically effective amount is about 80 mg.

Embodiment 18. The method of any one of embodiments 1-8, wherein the therapeutically effective amount is about 120 mg.

Embodiment 19. The method of any one of embodiments 1-8, wherein the therapeutically effective amount is any of 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, or 200 mg.

Embodiment 20. The method of any one of embodiments 1-8, wherein the therapeutically effective amount is any of 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, or about 200 mg.

Embodiment 21. The method of any one of embodiments 1-8, wherein the therapeutically effective amount is within the range of any of 25 mg to 200 mg, 40 mg to 200 mg, 60 mg to 200 mg, 80 mg to 200 mg, 100 mg to 200 mg, 120 mg to 200 mg, 150 mg to 200 mg, 25 mg to 120 mg, 30 mg to 120 mg, 40 mg to 120 mg, 60 mg to 120 mg, 80 mg to 120 mg, 40 mg to 80 mg, or 60 mg to 80 mg.

Embodiment 22. The method of any one of embodiments 1-8, wherein the therapeutically effective amount is any of 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, and less than 30 mg.

Embodiment 23. The method of any one of embodiments 1-8, wherein the therapeutically effective amount is any of 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, and less than about 30 mg.

Embodiment 24. The method of any one of embodiments 1-8, wherein the therapeutically effective amount is any of at least 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, at least 150 mg, at least 155 mg, at least 160 mg, at least 165 mg, at least 170 mg, at least 175 mg, at least 180 mg, at least 185, at least 190 mg, at least 195 mg, and at least 200 mg.

Embodiment 25. The method of any one of embodiments 1-8, wherein the therapeutically effective amount is any of 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, at least about 155 mg, at least about 160 mg, at least about 165 mg, at least about 170 mg, at least about 175 mg, at least about 180 mg, at least about 185, at least about 190 mg, at least about 195 mg, and at least about 200 mg.

Embodiment 26. The method of any one of embodiments 1-8, wherein the therapeutically effective amount is about 80 mg to about 120 mg.

Embodiment 27. The method of any one of embodiments 1-26, comprising administering the oligomeric compound once every week.

Embodiment 28. The method of any one of embodiments 1-26, comprising administering the oligomeric compound once every 2 weeks.

Embodiment 29. The method of any one of embodiments 1-26, comprising administering the oligomeric compound once every 3 weeks.

Embodiment 30. The method of any one of embodiments 1-26, comprising administering the oligomeric compound once every 4 weeks.

Embodiment 31. The method of any one of embodiments 1-26, comprising administering the oligomeric compound twice every week.

Embodiment 32. The method of any one of embodiments 1-26, comprising administering the oligomeric compound three times every week.

Embodiment 33. The method of any one of embodiments 1-26, comprising administering the oligomeric compound four times every week.

Embodiment 34. The method of any one of embodiments 1-26, comprising administering the oligomeric compound five times every week.

Embodiment 35. The method of any one of embodiments 1-26, comprising administering the oligomeric compound six times every week.

Embodiment 36. The method of any one of embodiments 1-26, comprising administering the oligomeric compound once every day, once every other day, once every 3 days, once every 4 days, once every 5 days, or once every 6 days.

Embodiment 37. The method of any one of embodiments 1-36, wherein at least one symptom of hypertension (HTN); resistant hypertension (RHTN); heart failure; chronic heart failure; heart failure with reduced ejection fraction (HFrEF); heart failure with preserved ejection fraction (HFpEF); diabetic nephropathy (DN); aortopathies associated with pathogenic TGF-β signaling; Marfan Syndrome; Loeys-Dietz Syndrome; Hereditary Hemorrhagic Telangiectasia; Familial Thoracic Aortic Aneurysm and Dissection; chronic kidney disease; hepatic steatosis; or atherosclerosis is reduced or improved.

Embodiment 38. The method of any one of embodiments 1-36, wherein the human subject has hypertension or resistant hypertension and at least one symptom of hypertension or resistant hypertension is reduced or improved.

Embodiment 39. The method of embodiment 38, wherein at least one symptom is headaches, nosebleeds, fatigue, confusion, vision problems, chest pain, difficulty breathing, irregular heartbeat, blood in urine, or a combination thereof.

Embodiment 40. The method of embodiment 38 or 39, wherein administering the oligomeric compound reduces blood pressure (BP), reduces systolic blood pressure (SBP), reduces diastolic blood pressure (DBP), achieves <140/90 mmHg BP, achieves <130/80 mmHg BP, improves quality of life as assessed by patient reported outcomes, or any combination thereof.

Embodiment 41. The method of any one of embodiments 1-36, wherein the human subject has heart failure and at least one symptom of heart failure is reduced or improved.

Embodiment 42. The method of embodiment 41, wherein at least one symptom is a symptom due to fluid volume excess including dyspnea, orthopnea, edema, hepatic congestion, and ascites; a symptom due to a diminished cardiac output including fatigue, dizziness, and weakness; or a combination thereof.

Embodiment 43. The method of embodiment 41 or 42, wherein administering the oligomeric compound reduces rates of cardiovascular (CV) mortality, reduces heart failure hospitalization and urgent visits, reduces N-terminal prohormone B-type natriuretic peptide (NT-proBNP) levels, reduces B-type natriuretic peptide (BNP) levels, reduces cardiac troponin T (cTnT) levels, reduces high-sensitive cardiac troponin T (hs-cTnT) levels, improves cardiac function, reduces cardiac dilation, reduces cardiac fibrosis, increases or improves LVEF (left ventricular ejection fraction), reduces or improves LVESV (left ventricular end systolic volume), reduces or improves LVEDV (left ventricular end diastolic volume), increases or improves left ventricle (LV) strain, improves 6 minute walk test, improves quality of life, or any combination thereof.

Embodiment 44. The method of any one of embodiments 1-36, wherein the human subject has Marfan syndrome and at least one symptom of Marfan syndrome is reduced or improved.

Embodiment 45. The method of embodiment 44, wherein administering the oligomeric compound reduces or improves aortic root dilation, mortality, aortic root surgery, or any combination thereof.

Embodiment 46. The method of any one of embodiments 1-45, wherein the oligomeric compound is administered by subcutaneous injection.

Embodiment 47. The method of embodiment 46, wherein the oligomeric compound is administered by a syringe.

I. AGT

In certain embodiments, described herein are methods of reducing AGT RNA and/or AGT protein in a cell or a biological fluid of a subject. AGT RNA is encoded by the human angiotensinogen (AGT) gene. AGT protein is the protein expression product of AGT RNA. A representative nucleobase sequence for a human *AGT* gene is the complement of the nucleotides of GenBank Accession No. NT_167186.1 truncated from nucleotides 24354000 to 24370100 (designated herein as SEQ ID NO: 1). A representative nucleobase sequence for a human AGT RNA is GENBANK Accession No. NM_000029.3 (designated herein as SEQ ID NO: 2).

II. ISIS 757456

In certain embodiments, a method comprises administering oligomeric compound, ISIS 757456, to a subject in need thereof.

In certain embodiments, ISIS 757456 is represented by the following chemical notation (5' to 3'): $GalNAc_3$-$7_{a\text{-}o}$mCes Aes mCes Aes Aes Ads mCds Ads Ads Gds mCds Tds Gds Gds Tds mCes Ges Ges Tes Te (SEQ ID NO: 3); wherein,

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

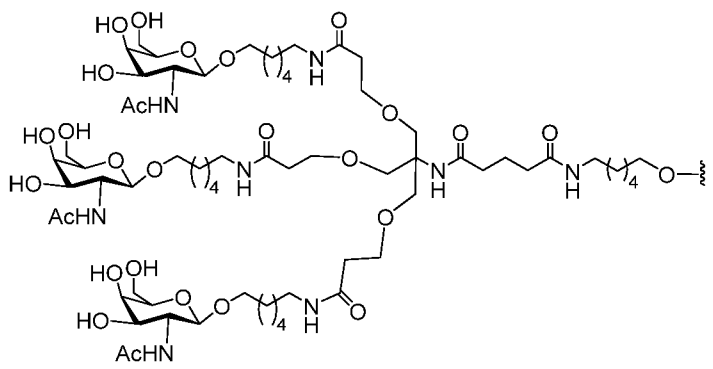
e = a 2'-MOE sugar moiety,

d = a 2'-β-D-deoxyribosyl sugar moiety,

s = a phosphorothioate internucleoside linkage,

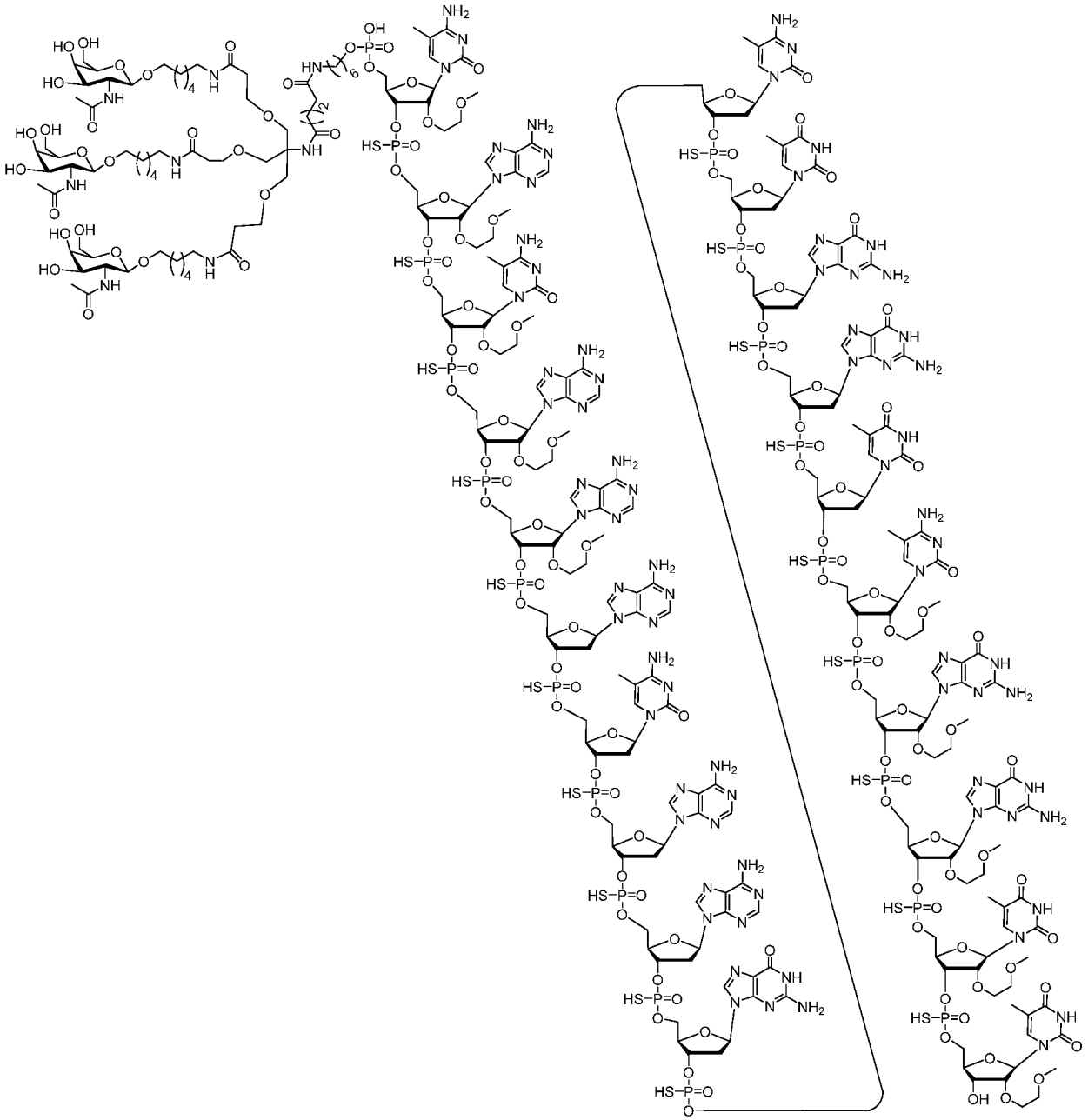
o' = 5'-P(OH)(=O)-O-3', and

$GalNAc_3$-7_a =



Structure 1. ISIS 757456

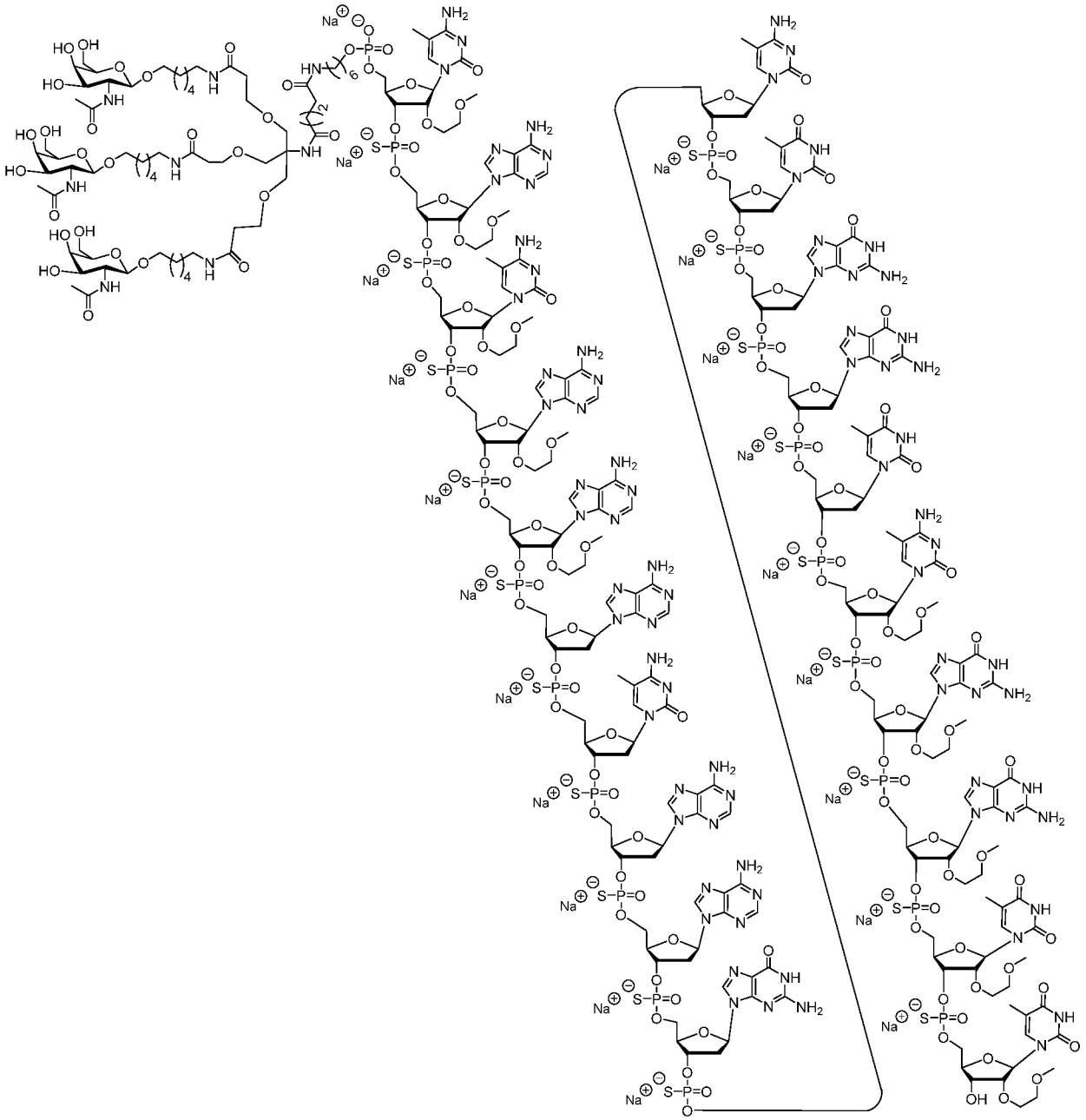
In certain embodiments, ISIS 757456 is represented by the following chemical structure:



(SEQ ID NO: 3).

Structure 2. Sodium salt of ISIS 757456

In certain embodiments, the sodium salt of ISIS 757456 is represented by the following chemical structure:



(SEQ ID NO: 3).

III. Certain Pharmaceutical Compositions

In certain embodiments, described herein are methods of administering to a subject a pharmaceutical composition comprising the oligomeric compound ISIS 757456. In certain embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable diluent or carrier. In certain embodiments, the pharmaceutical composition comprises or consists essentially of a sterile saline solution and the oligomeric compound ISIS 757456. In certain embodiments, the sterile saline is pharmaceutical grade saline. In certain embodiments, the pharmaceutical composition comprises or consists essentially of sterile water and the oligomeric compound ISIS 757456. In certain embodiments, the sterile water is pharmaceutical grade water.

In certain embodiments, the pharmaceutical composition comprises or consists essentially of the oligomeric compound ISIS 757456 in 2mM phosphate buffered isotonic saline, pH 7.4.

In certain embodiments, pharmaceutical compositions comprising the oligomeric compound ISIS 757456 encompass any pharmaceutically acceptable salt of the oligomeric compound ISIS 757456, esters of the oligomeric compound ISIS 757456, or salts of such esters. In certain embodiments, pharmaceutical compositions comprising the oligomeric compound ISIS 757456 are capable of providing (directly or indirectly) the biologically active metabolite or residue thereof upon administration to a human subject. Accordingly, for example, the disclosure is also drawn to pharmaceutically acceptable salts of the oligomeric compound ISIS 757456, prodrugs of the oligomeric compound ISIS 757456, pharmaceutically acceptable salts of such prodrugs, and other bioequivalents. Suitable pharmaceutically acceptable salts include, but are not limited to, sodium and potassium salts.

Under certain conditions, the oligomeric compound ISIS 757456 acts as an acid. Although ISIS 757456 may be drawn or described in protonated (free acid) form, or ionized and in association with a cation (salt) form, aqueous solutions of ISIS 757456 exist in equilibrium among such forms. For example, a phosphate linkage of ISIS 757456 in aqueous solution exists in equilibrium among free acid, anion, and salt forms. Unless otherwise indicated, the term, "ISIS 757456," is intended to include all such forms. Moreover, ISIS 757456 has several such linkages, each of which is in equilibrium. Thus, ISIS 757456 exists in solution in an ensemble of forms at multiple positions all at equilibrium. The term "ISIS 757456" 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 ISIS 757456 followed by the term "or a salt 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, ISIS 757456 is in aqueous solution with sodium. In certain embodiments, ISIS 757456 is in aqueous solution with potassium. In certain embodiments, ISIS 757456 is in PBS. In certain embodiments, ISIS 757456 is 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. For clarity, a dose of ISIS 757456 in milligrams indicates the mass of the free acid form of ISIS 757456. 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 ISIS 757456 exists as a solvent-free, sodium-acetate free, anhydrous, free acid. For example, where ISIS 757456 is in solution comprising sodium (e.g., saline), ISIS 757456 may be partially or fully de-protonated and in association with Na+ ions. However, the mass of the protons is 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 of 80 mg of ISIS 757456 equals the number of fully protonated molecules that weighs 80 mg. This would be equivalent to 83.8 mg of solvent-free, sodium-acetate free, anhydrous sodiated ISIS 757456.

In certain embodiments, ISIS 757456 is administered by subcutaneous injection. In certain embodiments, ISIS 757456 is administered by a syringe.

Certain Dosage Amounts

In certain embodiments, a method comprises administering to a subject a therapeutically effective amount of the oligomeric compound ISIS 757456. In certain embodiments, the therapeutically effective amount is 80 mg or about 80 mg. In certain embodiments, the therapeutically effective amount is 120 mg or about 120 mg. In certain embodiments, the therapeutically effective amount is administered once every week.

In certain embodiments, the therapeutically effective amount is 75 mg to 85 mg. In certain embodiments, the therapeutically effective amount is 110 mg to 130 mg or 115 mg to 125 mg. In certain embodiments, the therapeutically effective amount is administered once every week.

In certain embodiments, the therapeutically effective amount is any of 25 mg, 30 mg, 35 mg, 37.5 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, and 200 mg. In certain embodiments, the therapeutically effective amount is administered once every week.

In certain embodiments, the therapeutically effective amount is any of about 25 mg, about 30 mg, about 35 mg, about 37.5 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, and about 200 mg. In certain embodiments, the therapeutically effective amount is administered once every week.

In certain embodiments, the therapeutically effective amount is any of 25 mg to 200 mg, 25 mg to 80 mg, 40 mg to 80 mg, 40 mg to 120 mg, or 80 mg to 120 mg. In certain embodiments, the therapeutically effective amount is any of about 40 mg to about 80 mg, about 40 mg to about 120 mg, or about 80 mg to about 120 mg. In certain embodiments, the therapeutically effective amount is administered once every week.

In certain embodiments, the therapeutically effective amount is any of 40 mg to 200 mg, 40 mg to 190 mg, 40 mg to 180 mg, 40 mg to 170 mg, from 40 mg to 160 mg, 40 mg to 150 mg, 40 mg to 140 mg, 40 mg to 120 mg, 40 mg to 110 mg, 40 mg to 100 mg, 40 mg to 80 mg, 40 mg to 70 mg, 40 mg to 60 mg, 40 mg to 50 mg, 50 mg to 200 mg, 50 mg to 190 mg, 50 mg to 180 mg, 50 mg to 170 mg, 50 mg to 160 mg, 50 mg to 150 mg, 50 mg to 140 mg, 50 mg to 120 mg, 50 mg to 110 mg, 50 mg to 100 mg, 50 mg to 80 mg, 50 mg to 70 mg, 50 mg to 60 mg, 60 mg to 200 mg, 60 mg to 190 mg, 60 mg to 180 mg, 60 mg to 170 mg, 60 mg to 160 mg, 60 mg to 150 mg, 60 mg to 140 mg, 60 mg to 120 mg, 60 mg to 110 mg, 60 mg to 100 mg, 60 mg to 80 mg, 60 mg to 70 mg, 70 mg to 200 mg, 70 mg to 190 mg, 70 mg to 180 mg, 70 mg to 170 mg, 70 mg to 160 mg, 70 mg to 150 mg, 70 mg to 140 mg, 70 mg to 120 mg, 70 mg to 110 mg, 70 mg to 100 mg, 70 mg to 80

mg, 80 mg to 200 mg, 80 mg to 190 mg, 80 mg to 180 mg, 80 mg to 170 mg, 80 mg to 160 mg, 80 mg to 150 mg, 80 mg to 140 mg, 80 mg to 120 mg, 80 mg to 110 mg, 80 mg to 100 mg, 80 mg to 90 mg, 90 mg to 200 mg, 90 mg to 190 mg, 90 mg to 180 mg, 90 mg to 170 mg, 90 mg to 160 mg, 90 mg to 150 mg, 90 mg to 140 mg, 90 mg to 120 mg, 90 mg to 110 mg, 90 mg to 100 mg, 100 mg to 200 mg, 100 mg to 190 mg, 100 mg to 180 mg, 100 mg to 170 mg, 100 mg to 160 mg, 100 mg to 150 mg, 100 mg to 140 mg, 100 mg to 120 mg, 100 mg to 110 mg, 110 mg to 200 mg, 110 mg to 190 mg, 110 mg to 180 mg, 110 mg to 170 mg, 110 mg to 160 mg, 110 mg to 150 mg, 110 mg to 140 mg, 110 mg to 130 mg, 110 mg to 120 mg, 120 mg to 200 mg, 120 mg to 190 mg, 120 mg to 180 mg, 120 mg to 170 mg, 120 mg to 160 mg, 120 mg to 150 mg, 120 mg to 140 mg, 120 mg to 130 mg, 130 mg to 200 mg, 130 mg to 190 mg, 130 mg to 180 mg, 130 mg to 170 mg, 130 mg to 160 mg, 130 mg to 150 mg, 130 mg to 140 mg, 140 mg to 200 mg, 140 mg to 190 mg, 140 mg to 180 mg, 140 mg to 170 mg, 140 mg to 160 mg, 140 mg to 150 mg, 150 mg to 200 mg, 150 mg to 190 mg, 150 mg to 180 mg, 150 mg to 170 mg, 150 mg to 160 mg, 160 mg to 200 mg, 160 mg to 190 mg, 160 mg to 180 mg, 160 mg to 170 mg, 180 mg to 200 mg, 180 mg to 190 mg, 190 mg to 200 mg, 105 mg to 135 mg, 105 mg to 130 mg, 105 mg to 125 mg 105 mg to 120 mg, 110 mg to 135 mg, 110 mg to 130 mg, 110 mg to 125 mg, 110 mg to 120 mg, 115 mg to 135 mg, 115 mg to 130 mg, 115 mg to 125 mg, 115 mg to 120 mg, 115 mg to 125 mg, 115 mg to 120 mg, 120 mg to 135 mg, 120 mg to 125 mg, 125 mg to 140 mg, 125 mg to 130 mg, 130 mg to 135 mg, or 135 mg to 140 mg. In certain embodiments, the therapeutically effective amount is administered once every week.

In certain embodiments, the therapeutically effective amount is any of 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 and less than 30 mg. In certain embodiments, the therapeutically effective amount is administered once every week.

In certain embodiments, the therapeutically effective amount is any of 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, and less than about 30 mg. In certain embodiments, the therapeutically effective amount is administered once every week.

In certain embodiments, the therapeutically effective amount is any of 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 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, at least 150 mg, at least 155 mg, at least 160 mg, at least 165 mg, at least 170 mg, at least 175 mg, at least 180 mg, at least 185, at least 190 mg, at least 195 mg, and at least 200 mg. In certain embodiments, the therapeutically effective amount is administered once every week.

In certain embodiments, the therapeutically effective amount is any of 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, at least about 155 mg, at least about 160 mg, at least about 165 mg, at least about 170 mg, at least about 175 mg, at least about 180 mg, at least about 185, at least about 190 mg, at least about 195 mg, and at least about 200 mg. In certain embodiments, the therapeutically effective amount is administered once every week.

In certain embodiments a method comprises administering to a subject about 80 mg of the oligomeric compound ISIS 757456 once every week. In certain embodiments a method comprises administering to a subject 80 mg of the oligomeric compound ISIS 757456 once every week. In certain embodiments a method comprises administering to a subject about 120 mg of the oligomeric compound ISIS 757456 once every week. In certain embodiments a method comprises administering to a subject 120 mg of the oligomeric compound ISIS 757456 once every week. In certain embodiments a method comprises administering to a subject about 80 mg of the oligomeric compound ISIS 757456 subcutaneously once every week. In certain embodiments a method comprises administering to a subject 80 mg of the oligomeric compound ISIS 757456 administered subcutaneously once every week. In certain embodiments a method comprises administering to a subject about 120 mg of the oligomeric compound ISIS 757456 subcutaneously once every week. In certain embodiments a method comprises administering to a subject 120 mg of the oligomeric compound ISIS 757456 subcutaneously once every week.

IV. Certain Dosing Regimens

In certain embodiments, described herein are methods of administering to a subject a therapeutically effective amount of the oligomeric compound ISIS 757456 one or more times. In certain embodiments, methods comprise administering the therapeutically effective amount at least 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 times. In certain embodiments, methods comprise administering the therapeutically effective amount once every week. In certain embodiments, methods comprise administering the therapeutically effective amount once every other week.

In certain embodiments, methods comprise administering the therapeutically effective amount once

every week, once every 2 weeks, once every 3 weeks, once every 4 weeks, once every 5 weeks, once every 6 weeks, once every 7 weeks, or once every 8 weeks.

In certain embodiments, methods comprise administering the therapeutically effective amount once every week, twice every week, three times every week, four times every week, five times every week, or six times every week.

In certain embodiments, methods comprise administering the therapeutically effective amount once every day, once every 2 days, once every 3 days, once every 4 days, once every 5 days, or once every 6 days.

In certain embodiments, methods comprise administering the therapeutically effective amount for at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, or at least about 12 months.

In certain embodiments, methods comprise administering the therapeutically effective amount for as long as the subject needs treatment for hypertension (HTN); resistant hypertension (RHTN); heart failure; chronic heart failure; heart failure with reduced ejection fraction (HFrEF); heart failure with preserved ejection fraction (HFpEF); diabetic nephropathy (DN); aortopathies associated with pathogenic TGF-β signaling including, e.g., Marfan Syndrome, Loeys-Dietz Syndrome, Hereditary Hemorrhagic Telangiectasia, and Familial Thoracic Aortic Aneurysm and Dissection; chronic kidney disease; hepatic steatosis; or atherosclerosis.

Loading and Maintenance Doses

In certain embodiment, the therapeutically effective amount is administered as a loading dose and/or a maintenance dose. In certain embodiments, methods comprise administering a loading dose or doses and subsequently administering a maintenance dose or doses. In certain embodiments, methods comprise administering a loading dose once about every 4 weeks, and subsequently administering a maintenance dose once about every 8 weeks. In certain embodiments, methods comprise administering a loading dose once about every 4 weeks, and subsequently administering a maintenance dose once about every 16 weeks.

In certain embodiments, methods comprise administering at least 2 loading doses, at least 3 loading doses, at least 4 loading doses, at least 5 loading doses, or at least 6 loading doses. In certain embodiments, methods comprise administering 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16 loading doses. In certain embodiments, methods comprise administering a loading dose or doses about every 1 week, about every 2 weeks, about every 3 weeks, about every 4 weeks, about every 5 weeks, about every 6 weeks, about every 7 weeks, about every 8 weeks, about every 9 weeks, about every 10 weeks, about every 11 weeks, or about every 12 weeks. In certain embodiments, methods comprise administering an initial loading dose and administering a second loading dose about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, or about 12 weeks after

administering the initial loading dose.

In certain embodiments, methods comprise administering at least 2 maintenance doses, at least 3 maintenance doses, at least 4 maintenance doses, at least 5 maintenance doses, or at least 6 maintenance doses. In certain embodiments, methods comprise administering 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16 maintenance doses. In some instances, methods comprise administering a maintenance dose or doses about every 4 weeks, about every 5 weeks, about every 6 weeks, about every 7 weeks, about every 8 weeks, about every 9 weeks, about every 10 weeks, about every 11 weeks, about every 12 weeks, about every 13 weeks, about every 14 weeks, about every 15 weeks, about every 16 weeks, about every 17 weeks, about every 18 weeks, about every 19 weeks, or about every 20 weeks. In certain embodiments, methods comprise administering a first maintenance dose and administering a second maintenance dose about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, or about 20 weeks after administering the first maintenance dose.

In certain embodiments, methods comprise administering a first maintenance dose or doses about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, or about 20 weeks after administering the last loading dose.

In certain embodiments, methods comprise administering a loading dose of about 5 mg to about 120 mg of ISIS 757456 in the same week as administering a maintenance dose of about 5 mg to about 120 mg of ISIS 757456. In certain embodiments, the loading dose is about 5, 10, 20, 40, 60, 80 or 120 mg of ISIS 757456. In certain embodiments, the maintenance dose is about 5, 10, 20, 40, 60, 80 or 120 mg of ISIS 757456. In certain embodiments, the loading dose is about 80 mg of ISIS 757456. In certain embodiments, the maintenance dose is about 80 mg of ISIS 757456. In certain embodiments, the loading dose is about 120 mg of ISIS 757456. In certain embodiments, the maintenance dose is about 120 mg of ISIS 757456. In certain embodiments, the loading dose is administered for 1 week and the maintenance dose is administered for as long as the human subject needs treatment.

Dose Titration

Certain embodiments are drawn to administering a first dose of ISIS 757456 for a first period of time followed by a second dose of ISIS 757456 for a second period of time, wherein the second dose is smaller than the first dose. In certain embodiments, the first period of time and the second period of time do not overlap.

In certain embodiments, a method comprises administering to a subject about 120 mg of ISIS 757456 for a first period of time followed by administering to the subject about 5 mg, about 10 mg, about 20 mg, about 40 mg, about 60 mg, or about 80 mg of ISIS 757456 for a second period of time. In certain embodiments, a

method comprises administering to a subject about 120 mg of ISIS 757456 once every week for a first period of time followed by administering to the subject about mg, about 10 mg, about 20 mg, about 40 mg, about 60 mg, or about 80 mg of ISIS 757456 once every week for a second period of time. In certain embodiments, the first period of time and the second period of time do not overlap.

In certain embodiments, a method comprises administering to a subject about 80 mg of ISIS 757456 for a first period of time followed by administering to the subject about 5 mg, about 10 mg, about 20 mg, about 40 mg, or about 60 mg of ISIS 757456 for a second period of time. In certain embodiments, a method comprises administering to a subject about 80 mg of ISIS 757456 once every week for a first period of time followed by administering to the subject about 5 mg, about 10 mg, about 20 mg, about 40 mg, about 60 mg, or about 80 mg of ISIS 757456 once every week for a second period of time. In certain embodiments, the first period of time and the second period of time do not overlap.

V. Certain Combination Therapies

In certain embodiments, methods comprise co-administering ISIS 757456 with at least one other pharmaceutical agent. In certain embodiments, the at least one other pharmaceutical agent treats hypertension (HTN); resistant hypertension (RHTN); heart failure; chronic heart failure; heart failure with reduced ejection fraction (HFrEF); heart failure with preserved ejection fraction (HFpEF); diabetic nephropathy (DN); aortopathies associated with pathogenic TGF-β signaling including, e.g., Marfan Syndrome, Loeys-Dietz Syndrome, Hereditary Hemorrhagic Telangiectasia, and Familial Thoracic Aortic Aneurysm and Dissection; chronic kidney disease; hepatic steatosis; or atherosclerosis, or a symptom thereof. In certain embodiments, ISIS 757456 is co-administered with the at least one other pharmaceutical agent to produce a combinational effect. In certain embodiments, ISIS 757456 is co-administered with the at least one other pharmaceutical agent to produce a synergistic effect.

In certain embodiments, ISIS 757456 and the at least one other pharmaceutical agent are administered at the same time. In certain embodiments, ISIS 757456 and the at least one other pharmaceutical agent are administered at different times. In certain embodiments, ISIS 757456 and the at least one other pharmaceutical agent are prepared together in a single formulation. In certain embodiments, ISIS 757456 and the at least one other pharmaceutical agent are administered are prepared separately.

In certain embodiments, pharmaceutical agents that may be co-administered with ISIS 757456 include angiotensin-converting enzyme inhibitor (ACEi, e.g., lisinopril, ramipril, perindopril, enalapril, benazepril, quinapril, captopril, fosinopril, trandolapril, moexipril, enalaprilat), angiotensin II receptor blocker (ARB, e.g., losartan, olmesartan, valsartan, candesartan, irbesartan, telmisartan, azilsartan, eprosartan), beta blocker, calcium channel blocker, non-potassium sparing diuretic, alpha-1 blocker, centrally acting sympatholytic agent, SGLT2 inhibitor (SGLT2i, e.g., empaglifozin, canaglifozin, dapaglifozin, ertuglifozin), or direct acting vasodilators (e.g. hydralazine), neprilysin inhibitor (e.g., sacubitril).

VI. Certain Indications

Any of the foregoing methods, doses, or dosing regimens can be used for treating hypertension (HTN); resistant hypertension (RHTN); heart failure; chronic heart failure; heart failure with reduced ejection fraction (HFrEF); heart failure with preserved ejection fraction (HFpEF); diabetic nephropathy (DN); aortopathies associated with pathogenic TGF-β signaling including, e.g., Marfan Syndrome, Loeys-Dietz Syndrome, Hereditary Hemorrhagic Telangiectasia, and Familial Thoracic Aortic Aneurysm and Dissection; chronic kidney disease; hepatic steatosis; or atherosclerosis. In certain embodiments, methods, doses, or dosing regimens described herein can be used for treating RHTN in a subject who has failed to achieve a blood pressure <140/90 mmHg despite taking or having taken 3 or more medications for hypertension. In certain embodiments, methods, doses, or dosing regimens described herein can be used for treating RHTN in a subject who has failed to achieve a blood pressure <130/80 mmHg despite taking or having taken 3 or more medications for hypertension. In certain embodiments, the 3 or more medications for hypertension belong to one or more of the following classes of medications: a diuretic, a long-acting calcium channel blocker, a beta blocker, or a renin-angiotensin pathway blocker such as an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker. In certain embodiments, administering ISIS 757456 in any of the foregoing doses or dosing regimens can improve or reduce at least one symptom in a subject have any of the aforementioned diseases.

VII. Efficacy

Assessing Efficacy of ISIS 757456

In certain embodiments, methods described herein are sufficiently effective to treat hypertension (HTN); resistant hypertension (RHTN); heart failure; chronic heart failure; heart failure with reduced ejection fraction (HFrEF); heart failure with preserved ejection fraction (HFpEF); diabetic nephropathy (DN); aortopathies associated with pathogenic TGF-β signaling including, e.g., Marfan Syndrome, Loeys-Dietz Syndrome, Hereditary Hemorrhagic Telangiectasia, and Familial Thoracic Aortic Aneurysm and Dissection; chronic kidney disease; hepatic steatosis; or atherosclerosis in a human subject.

In certain embodiments, methods described herein improves symptoms of a human subject having hypertension (HTN); resistant hypertension (RHTN); heart failure; chronic heart failure; heart failure with reduced ejection fraction (HFrEF); heart failure with preserved ejection fraction (HFpEF); diabetic nephropathy (DN); aortopathies associated with pathogenic TGF-β signaling including, e.g., Marfan Syndrome, Loeys-Dietz Syndrome, Hereditary Hemorrhagic Telangiectasia, and Familial Thoracic Aortic Aneurysm and Dissection; chronic kidney disease; hepatic steatosis; or atherosclerosis.

In certain embodiments, a method of treating hypertension or resistant hypertension comprises administering a therapeutically effective amount of ISIS 757456 to a subject having hypertension or resistant hypertension, thereby treating hypertension or resistant hypertension in the subject. In certain embodiments, administering a therapeutically effective amount of ISIS 757456 to a subject having hypertension or resistant hypertension reduces blood pressure (BP), reduces systolic blood pressure (SBP), reduces diastolic blood pressure (DBP), achieves <140/90 mmHg BP, achieves <130/80 mmHg BP, improves quality of life as assessed

by patient reported outcomes, or any combination thereof, in the subject. In certain embodiments, administering a therapeutically effective amount of ISIS 757456 to a subject having hypertension or resistant hypertension reduces or improves headaches, nosebleeds, fatigue, confusion, vision problems, chest pain, difficulty breathing, irregular heartbeat, blood in urine, or any combination thereof, in the subject.

In certain embodiments, a method of treating hypertension or resistant hypertension comprises administering a therapeutically effective amount of ISIS 757456 once a week to a subject having hypertension or resistant hypertension, thereby treating hypertension or resistant hypertension in the subject. In certain embodiments a method of treating hypertension or resistant hypertension comprises administering to a subject having hypertension or resistant hypertension about 80 mg of the oligomeric compound ISIS 757456 once every week. In certain embodiments a method of treating hypertension or resistant hypertension comprises administering to a subject having hypertension or resistant hypertension 80 mg of the oligomeric compound ISIS 757456 once every week. In certain embodiments a method of treating hypertension or resistant hypertension comprises administering to a subject having hypertension or resistant hypertension about 120 mg of the oligomeric compound ISIS 757456 once every week. In certain embodiments a method of treating hypertension or resistant hypertension comprises administering to a subject having hypertension or resistant hypertension 120 mg of the oligomeric compound ISIS 757456 once every week. In certain embodiments a method of treating hypertension or resistant hypertension comprises administering to a subject having hypertension or resistant hypertension about 80 mg of the oligomeric compound ISIS 757456 subcutaneously once every week. In certain embodiments a method of treating hypertension or resistant hypertension comprises administering to a subject having hypertension or resistant hypertension 80 mg of the oligomeric compound ISIS 757456 subcutaneously once every week. In certain embodiments a method of treating hypertension or resistant hypertension comprises administering to a subject having hypertension or resistant hypertension about 120 mg of the oligomeric compound ISIS 757456 subcutaneously once every week. In certain embodiments a method of treating hypertension or resistant hypertension comprises administering to a subject having hypertension or resistant hypertension 120 mg of the oligomeric compound ISIS 757456 subcutaneously once every week.

In certain embodiments, a method of treating hypertension or resistant hypertension comprises administering a therapeutically effective amount of ISIS 757456 to a subject having uncontrolled hypertension on two or three or more antihypertensive medications, thereby treating hypertension or resistant hypertension in the subject. In certain embodiments a method of treating hypertension or resistant hypertension comprises administering to a subject having uncontrolled hypertension on two or three antihypertensive medications 80 mg of the oligomeric compound ISIS 757456 once every week. In certain embodiments a method of treating hypertension or resistant hypertension comprises administering to a subject having uncontrolled hypertension on two or three antihypertensive medications about 120 mg of the oligomeric compound ISIS 757456 once every week. In certain embodiments a method of treating hypertension or resistant hypertension comprises administering to a subject having uncontrolled hypertension on two or three antihypertensive medications 120

mg of the oligomeric compound ISIS 757456 once every week. In certain embodiments a method of treating hypertension or resistant hypertension comprises administering to a subject having uncontrolled hypertension on two or three antihypertensive medications about 80 mg of the oligomeric compound ISIS 757456 subcutaneously once every week. In certain embodiments a method of treating hypertension or resistant hypertension comprises administering to a subject having uncontrolled hypertension on two or three antihypertensive medications 80 mg of the oligomeric compound ISIS 757456 subcutaneously once every week. In certain embodiments a method of treating hypertension or resistant hypertension comprises administering to a subject having uncontrolled hypertension on two or three antihypertensive medications about 120 mg of the oligomeric compound ISIS 757456 subcutaneously once every week. In certain embodiments a method of treating hypertension or resistant hypertension comprises administering to a subject having uncontrolled hypertension on two or three antihypertensive medications 120 mg of the oligomeric compound ISIS 757456 subcutaneously once every week.

In certain embodiments, a method of treating heart failure comprises administering a therapeutically effective amount of ISIS 757456 to a subject having heart failure, thereby treating heart failure in the subject. In certain embodiments, administering a therapeutically effective amount of ISIS 757456 to a subject having heart failure reduces rates of cardiovascular (CV) mortality, reduces heart failure hospitalization and urgent heart failure visits, reduces N-terminal prohormone B-type natriuretic peptide (NT-proBNP) levels, reduces B-type natriuretic peptide (BNP) levels, reduces cardiac troponin T (cTnT) levels, reduces high-sensitive cardiac troponin T (hs-cTnT) levels, improves cardiac function, reduces cardiac dilation, reduces cardiac fibrosis, increases or improves LVEF (left ventricular ejection fraction), reduces or improves LVESV (left ventricular end systolic volume), reduces or improves LVEDV (left ventricular end diastolic volume), increases or improves left ventricle (LV) strain, improves 6 minute walk test, improves quality of life, or any combination thereof, in the subject.

In certain embodiments, a method of treating heart failure comprises administering a therapeutically effective amount of ISIS 757456 once a week to a subject having heart failure, thereby treating heart failure in the subject. In certain embodiments, administering a therapeutically effective amount of ISIS 757456 to a subject having heart failure reduces or improves symptoms due to fluid volume excess including dyspnea, orthopnea, edema, hepatic congestion, and ascites; reduces or improves symptoms due to a diminished cardiac output including fatigue, dizziness, and weakness; or any combination thereof, in the subject. In certain embodiments a method of treating heart failure comprises administering to a subject having heart failure about 80 mg of the oligomeric compound ISIS 757456 once every week. In certain embodiments a method of treating heart failure comprises administering to a subject having heart failure 80 mg of the oligomeric compound ISIS 757456 once every week. In certain embodiments a method of treating heart failure comprises administering to a subject having heart failure about 120 mg of the oligomeric compound ISIS 757456 once every week. In certain embodiments a method of treating heart failure comprises administering to a subject having heart failure 120 mg of the oligomeric compound ISIS 757456 once every week. In certain embodiments a method of

treating heart failure comprises administering to a subject having heart failure about 80 mg of the oligomeric compound ISIS 757456 subcutaneously once every week. In certain embodiments a method of treating heart failure comprises administering to a subject having heart failure 80 mg of the oligomeric compound ISIS 757456 subcutaneously once every week. In certain embodiments a method of treating heart failure comprises administering to a subject having heart failure about 120 mg of the oligomeric compound ISIS 757456 subcutaneously once every week. In certain embodiments a method of treating heart failure comprises administering to a subject having heart failure 120 mg of the oligomeric compound ISIS 757456 subcutaneously once every week.

In certain embodiments, a method of treating heart failure comprises administering a therapeutically effective amount of ISIS 757456 to a subject having chronic heart failure with reduced ejection fraction, thereby treating chronic heart failure in the subject. In certain embodiments a method of treating heart failure comprises administering to a subject having chronic heart failure with reduced ejection fraction about 80 mg of the oligomeric compound ISIS 757456 once every week. In certain embodiments a method of treating heart failure comprises administering to a subject having chronic heart failure with reduced ejection fraction 80 mg of the oligomeric compound ISIS 757456 once every week. In certain embodiments a method of treating heart failure comprises administering to a subject having chronic heart failure with reduced ejection fraction about 120 mg of the oligomeric compound ISIS 757456 once every week. In certain embodiments a method of treating heart failure comprises administering to a subject having chronic heart failure with reduced ejection fraction 120 mg of the oligomeric compound ISIS 757456 once every week. In certain embodiments a method of treating heart failure comprises administering to a subject having chronic heart failure with reduced ejection fraction about 80 mg of the oligomeric compound ISIS 757456 subcutaneously once every week. In certain embodiments a method of treating heart failure comprises administering to a subject having chronic heart failure with reduced ejection fraction 80 mg of the oligomeric compound ISIS 757456 subcutaneously once every week. In certain embodiments a method of treating heart failure comprises administering to a subject having chronic heart failure with reduced ejection fraction about 120 mg of the oligomeric compound ISIS 757456 subcutaneously once every week. In certain embodiments a method of treating heart failure comprises administering to a subject having chronic heart failure with reduced ejection fraction failure 120 mg of the oligomeric compound ISIS 757456 subcutaneously once every week.

In certain embodiments, a method of treating Marfan syndrome comprises administering a therapeutically effective amount of ISIS 757456 to a subject having Marfan syndrome, thereby treating Marfan syndrome in the subject. In certain embodiments, administering a therapeutically effective amount of ISIS 757456 to a subject having Marfan syndrome reduces or improves aortic root dilation, mortality, aortic root surgery, or any combination thereof, in the subject.

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.

Example 1: Phase 1 Human Clinical Trial with ISIS 757456 in Healthy Volunteers

The phase 1 trial in healthy volunteers was a randomized, double-blind, placebo-controlled study assessing safety and tolerability of ISIS 757456 in 5 single-ascending dose cohorts (5-80 mg) and 2 multiple-ascending dose cohorts dosed weekly for 6-weeks (40 to 80 mg in an 8:2 randomization ratio). Subjects with a screening plasma AGT level < 20 μg/mL were not eligible for the multiple-dose cohorts. The primary objective was to assess safety and tolerability. Plasma AGT levels over time were also measured.

In the phase 1 Healthy Volunteer Study, single ascending doses (29 subjects treated with ISIS 757456 and 12 with placebo) and multiple ascending doses (16 subjects treated with ISIS 757456 and 4 with placebo), were well tolerated with no drug related SAEs, no clinically meaningful changes in laboratory assessments, no hypotensive events, acute renal changes or hyperkalemia. Six weeks of treatment resulted in significant and dose-dependent reductions in AGT (46%, p=0.004 and 60%, p=0.006 mean reductions in the 40 mg and 80 mg groups respectively). Plasma AGT levels returned to baseline levels 10 weeks after the last dose. There was no significant effect on blood pressure, Ang II, brain natriuretic peptide, atrial natriuretic peptide or renin mass and activity.

ISIS 757456 results in significant AGT reductions with favorable safety and tolerability profile. As monotherapy, proof of principle was demonstrated as evidenced by reduction in systolic blood pressure (SBP) thereby providing support to proceed to larger phase 2 trials in patients with resistant hypertension and heart failure.

Example 2: Phase 2 Human Clinical Trial with ISIS 757456 Monotherapy in Patients with Hypertension

The phase 2 monotherapy study was a randomized, double-blind, placebo-controlled trial evaluating ISIS 757456. Patients aged 18-72 years, inclusive, with controlled hypertension on 2 antihypertensive medications , one of which was an ACEi or an ARB and the other was either a beta blocker, calcium channel blocker, or diuretic, were enrolled. Patients with a screening plasma AGT level <20 μg/mL or with K+ >4.85 and UPCR >=0.3 mg/mg were excluded. All anti-hypertensive medications were stopped for 14 days (Wash-Out). Patients who met the inclusion criteria of a systolic blood pressure (SBP) >140 - ≤165 mmHg after Wash-Out were randomized 2:1 to 80 mg ISIS 757456 or placebo. Patients were also stratified by screening plasma AGT level (≤30 μg/mL vs. >30 μg/mL). All patients received weekly, in-clinic, subcutaneous injections for 6 weeks with a loading dose administered on Day 3, then followed for 12 weeks in the post treatment period. The primary efficacy endpoint was the comparison of percent change in plasma AGT from baseline to study week 7 (Day 43) between 80 mg ISIS 757456 and placebo. Exploratory endpoints included post-baseline changes in SBP, diastolic blood pressure (DBP), percentage of patients reaching the goals of in-clinic SBP ≤ 140 mmHg, DBP ≤ 90 mmHg, and both over time. Blood pressure was

measured by study personnel at every in-clinic visit in a quiet room after 5 minutes of resting in a chair with feet on the floor. Three consecutive blood pressure measurements were averaged to obtain an average blood pressure.

At screening the mean (SD) AGT levels were 27.4 (13.1) μg/mL in the placebo group and 23.5 (3.7) μg/ml in the ISIS 757456 group (p=0.80). All patients had confirmed controlled SBP/DBP on HTN therapy at Screening. The AGT levels tended to decline following Wash-Out of anti-hypertensive medications. An expected, a rise in blood pressure occurred after stopping the anti-hypertensive medications for 14 days, reaching mean SBP 149 mmHg and 146 mmHg and DBP 88 and 86 mmHg for the placebo and ISIS 757456 groups, respectively. Renal function and potassium levels were normal at baseline.

ISIS 757456 was well tolerated with no hypotensive events, hyperkalemia or renal abnormalities (Supplemental Table 3). After 6 weeks of dosing at Day 43, a significant mean absolute reduction in AGT levels was noted in the ISIS 757456 group compared to placebo (-11.2 μg/mL versus 2.0, $p<0.001$). Similarly, the mean percent reduction in AGT levels was significantly lower with ISIS 757456 compared to placebo (-54% versus 12.6%, $p<0.001$). In the ISIS 757456 group, 6 treated patients had AGT levels below the lower level of detection of the assay and were assigned values of 4.7 μg/ml. The reductions were sustained and demonstrated reversibility in the post treatment period.

There was a numerically larger reduction in in SBP (-8 mmHg) or DBP (-1 mmHg) observed with ISIS 757456 compared to placebo but these did not reach statistical significance. A higher percentage of subjects treated with ISIS 757456 compared to placebo achieved ≥5, ≥10 and ≥15 mmHg reductions in SBP and DBP. Similarly, a higher percentage of patients treated with ISIS 757456 compared to placebo reached SBP ≤140 mmHg or DBP ≤90 mmHg. There were no significant changes in ANGII, aldosterone, or renin mass or activity.

ISIS 757456 results in significant AGT reductions with favorable trends in SBP and DBP reduction in subjects with uncontrolled HTN with concomitant RAAS blockade. No on-target effects were observed. A dose-ranging, Phase 2B study is underway in subjects with resistant HTN on 3 medications, as well a Phase 2 study in patients with heart failure with reduced ejection fraction.

Example 3: Phase 2 Human Clinical Trial with ISIS 757456 in Patients with Uncontrolled Hypertension on Two or Three Antihypertensive Medications

A phase 2 randomized, double-blind, placebo-controlled add-on trial evaluating ISIS 757456 was conducted. Patients aged 18-75 years, inclusive, on a stable regimen of 2 to 3 antihypertensive medications, including an ACEi or ARB and 1 or 2 additional antihypertensives in the beta blocker, calcium channel blocker, or non-potassium sparing diuretic classes were eligible. The inclusion criteria also required that patients have an average SBP within >140 and ≤170 mmHg and DBP >80 mmHg at screening and pre-dose Day 1. Subjects with a screening AGT level <20 μg/mL or with K+ >4.9 and UPCR >=0.3 mg/mg were excluded. Patients were stratified by screening ACEi or ARB dose then randomized 2:1 to 80 mg ISIS 757456 or placebo, respectively.

All patients received weekly in-clinic subcutaneous injections for 8 weeks with a loading dose administered on Day 3, then followed for 12 weeks in the post treatment period. The primary efficacy endpoint was the comparison of percent change from baseline to study week 9 (Day 57) in plasma AGT between 80 mg ISIS 757456 and placebo. Exploratory endpoints included post-baseline changes in SBP, DBP and percentage of patients reaching goals of SPB ≤140 mmHg, DBP ≤80 mmHg and both during the study. Blood pressure was measured as in the Example 2.

Baseline mean AGT levels were 25.5 and 25.2 μg/mL in the placebo and ISIS 757456 groups, respectively. Approximately two thirds of patients were taking 2 anti-hypertensive medications and one third 3 antihypertensive medications. Baseline mean SBP was 152 mmHg and DBP 87 in the placebo group and SBP 154 and DBP 89 mmHg in the ISIS 757456 group.

ISIS 757456 was well tolerated with no serious adverse events, hypotensive events or renal abnormalities. After 8 weeks of dosing at Day 57, a significant absolute reduction in mean AGT levels was noted in the ISIS 757456 group compared to placebo (-17.0 versus -1.1 μg/mL $p<0.001$). Similarly, the mean percent reduction in AGT levels was significantly lower in ISIS 757456 compared to placebo (67% versus 3.4%, $p<0.001$). In the ISIS 757456 group, 2 treated patients had AGT levels below the lower level of detection and were assigned values of 4.7 μg/ml.

There was a numerically larger reduction in SBP (-12 mmHg) and DBP (-6 mmHg) observed with ISIS 757456 compared to placebo but these did not reach statistical significance. A higher percentage of subjects treated with ISIS 757456 compared to placebo achieved ≥5, ≥10 and ≥15 mmHg reductions in SBP and DBP. Similarly, a higher percentage of patients treated with ISIS 757456 compared to placebo reached SBP ≤140 mmHg or DBP ≤90 mmHg. There was no significant difference based on whether patients were on 2 or 3 anti-hypertensive medications. There were no significant changes in ANGII, aldosterone or renin mass or activity.

Example 4: Phase 2 Human Clinical Trial to Assess the Safety, Tolerability and Efficacy of ISIS 757456 Administered to Hypertensive Patients with Uncontrolled Blood Pressure

A Phase 2 study to evaluate the effect of ISIS 757456 compared to placebo on seated automated office systolic blood pressure (SBP) from Baseline in uncontrolled hypertensive patients on 3 or more antihypertensive medications in the following categories is conducted: angiotensin-converting enzyme inhibitor (ACEi), angiotensin II receptor blocker (ARB), beta blocker, calcium channel blocker, non-potassium sparing diuretic, alpha-1 blocker, centrally acting sympatholytic agent, or direct acting vasodilators (e.g. hydralazine). 80 mg or 120 mg of ISIS 757456 is administered to the patients once every week. The following are evaluated:

The effect of ISIS 757456 on plasma angiotensinogen (AGT) at each scheduled visit in uncontrolled hypertensive patients on ≥ 3 antihypertensive medications.

The effect of ISIS 757456 on 24-hour ambulatory blood pressure at Study Day 85 in uncontrolled hypertensive patients on ≥ 3 antihypertensive medications.

The effect of ISIS 757456 on seated automated office SBP at each scheduled visit in uncontrolled hypertensive patients on ≥ 3 antihypertensive medications.

The effect of ISIS 757456 on seated automated office diastolic blood pressure (DBP) at each scheduled visit in uncontrolled hypertensive patients on ≥ 3 antihypertensive medications

Example 5: Phase 2 Human Clinical Trial Assessing the Safety, Tolerability and Efficacy of ISIS 757456 in Patients with Chronic Heart Failure with Reduced Ejection Fraction

The effect of ISIS 757456, weekly subcutaneous (SC) injection on plasma angiotensinogen (AGT) concentration from Baseline to Study Day 85 (Week 13) in patients with chronic heart failure (HF) with reduced ejection fraction (HFrEF) is evaluated. 40 mg or 80 mg or 120 mg of ISIS 757456 is administered to the patients once weekly. The following are evaluated:

The effect of ISIS 757456 weekly SC injection on plasma angiotensinogen (AGT) concentration at each scheduled visit in patients with chronic HFrEF.

The effect of ISIS 757456 on N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) at each scheduled visit in patients with chronic HFrEF.

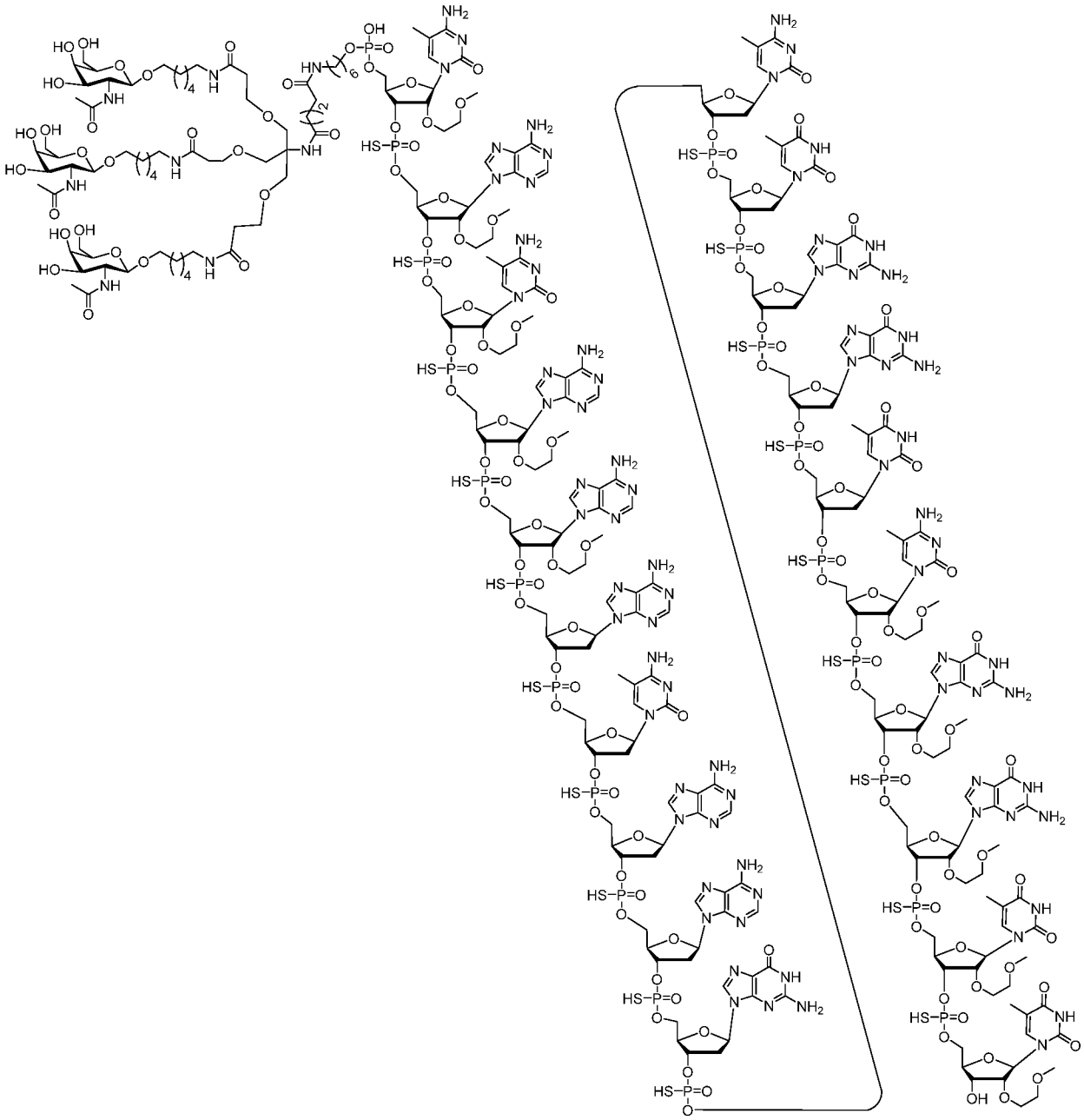
The effect of ISIS 757456 on high sensitivity cardiac troponin T (hs-cTnT) at each scheduled visit in patients with chronic HFrEF.

The effect of ISIS 757456 on functional capacity, patient-reported outcomes and disease scores related to the quality of life (QOL) at each scheduled visit in patients with chronic HFrEF.

The effect of ISIS 757456 on clinical outcomes in patients with HFrEF.

CLAIMS:

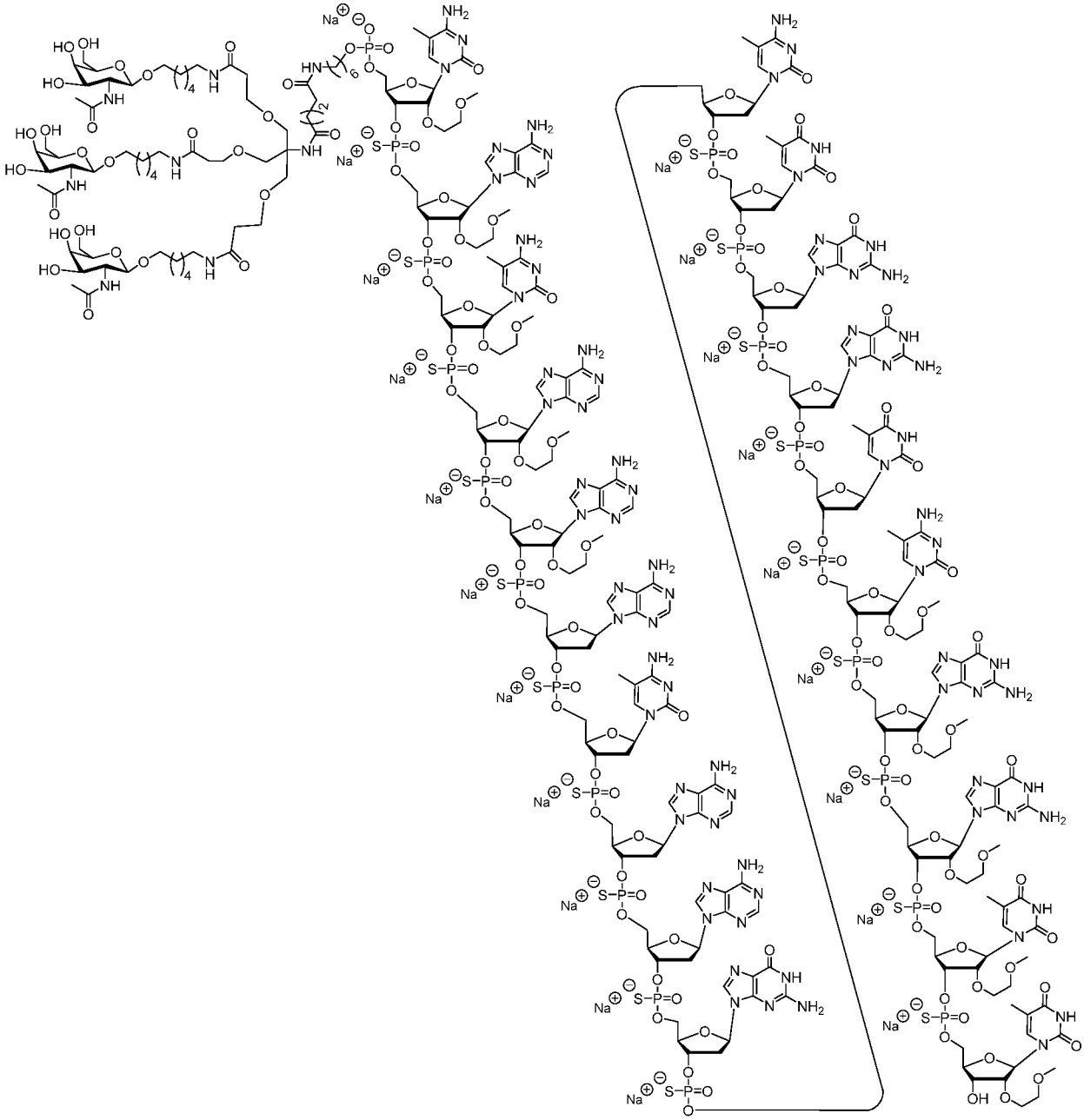
1. A method of treating hypertension (HTN); resistant hypertension (RHTN); heart failure; chronic heart failure; heart failure with reduced ejection fraction (HFrEF); heart failure with preserved ejection fraction (HFpEF); diabetic nephropathy (DN); aortopathies associated with pathogenic TGF-β signaling; Marfan Syndrome; Loeys-Dietz Syndrome; Hereditary Hemorrhagic Telangiectasia; Familial Thoracic Aortic Aneurysm and Dissection; chronic kidney disease; hepatic steatosis; or atherosclerosis in a human subject comprising administering to the human subject a therapeutically effective amount of an oligomeric compound according to the following chemical structure:



(SEQ ID NO: 3), or a salt thereof.

2. The method of claim 1, wherein the oligomeric compound is the sodium salt or the potassium salt.

3. A method of treating hypertension (HTN); resistant hypertension (RHTN); heart failure; chronic heart failure; heart failure with reduced ejection fraction (HFrEF); heart failure with preserved ejection fraction (HFpEF); diabetic nephropathy (DN); aortopathies associated with pathogenic TGF-β signaling; Marfan Syndrome; Loeys-Dietz Syndrome; Hereditary Hemorrhagic Telangiectasia; Familial Thoracic Aortic Aneurysm and Dissection; chronic kidney disease; hepatic steatosis; or atherosclerosis in a human subject comprising administering to the human subject a therapeutically effective amount of an oligomeric compound according to the following chemical structure:



(SEQ ID NO: 3).

4. A method of treating hypertension (HTN); resistant hypertension (RHTN); heart failure; chronic heart failure; heart failure with reduced ejection fraction (HFrEF); heart failure with preserved ejection fraction (HFpEF); diabetic nephropathy (DN); aortopathies associated with pathogenic TGF-β signaling; Marfan Syndrome; Loeys-Dietz Syndrome; Hereditary Hemorrhagic Telangiectasia; Familial Thoracic Aortic Aneurysm and Dissection; chronic kidney disease; hepatic steatosis; or atherosclerosis in a human subject comprising administering to the human subject a therapeutically effective amount of an oligomeric compound comprising a modified oligonucleotide and a conjugate group according to the following formula: $GalNAc_3$-$7_{a\text{-}o}$ mCes Aes mCes Aes Aes Ads mCds Ads Ads Gds mCds Tds Gds Gds Tds mCes Ges Ges Tes Te (SEQ ID NO: 3); wherein,

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

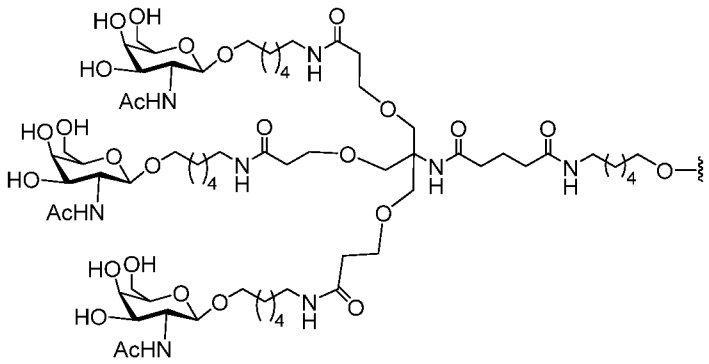
e = a 2'-MOE sugar moiety,

d = a 2'-β-D-deoxyribosyl sugar moiety,

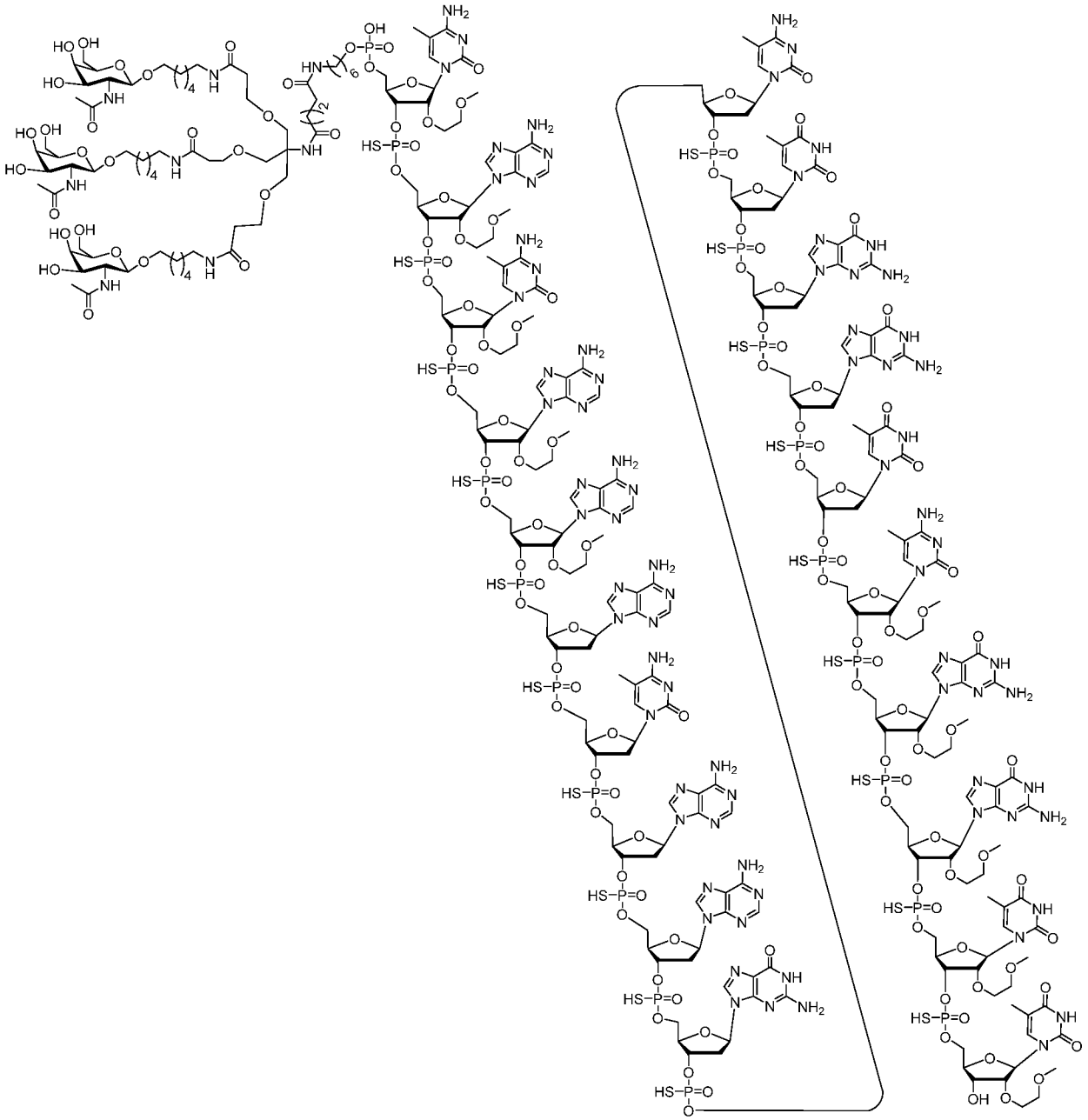
s = a phosphorothioate internucleoside linkage,

o' = 5'-P(OH)(=O)-O-3', and

$GalNAc_3$-7_a =



5. A method of reducing AGT RNA or protein in a human subject having hypertension (HTN); resistant hypertension (RHTN); heart failure; chronic heart failure; heart failure with reduced ejection fraction (HFrEF); heart failure with preserved ejection fraction (HFpEF); diabetic nephropathy (DN); aortopathies associated with pathogenic TGF-β signaling; Marfan Syndrome; Loeys-Dietz Syndrome; Hereditary Hemorrhagic Telangiectasia; Familial Thoracic Aortic Aneurysm and Dissection; chronic kidney disease; hepatic steatosis; or atherosclerosis comprising administering to the human subject a therapeutically effective amount of an oligomeric compound according to the following chemical structure:

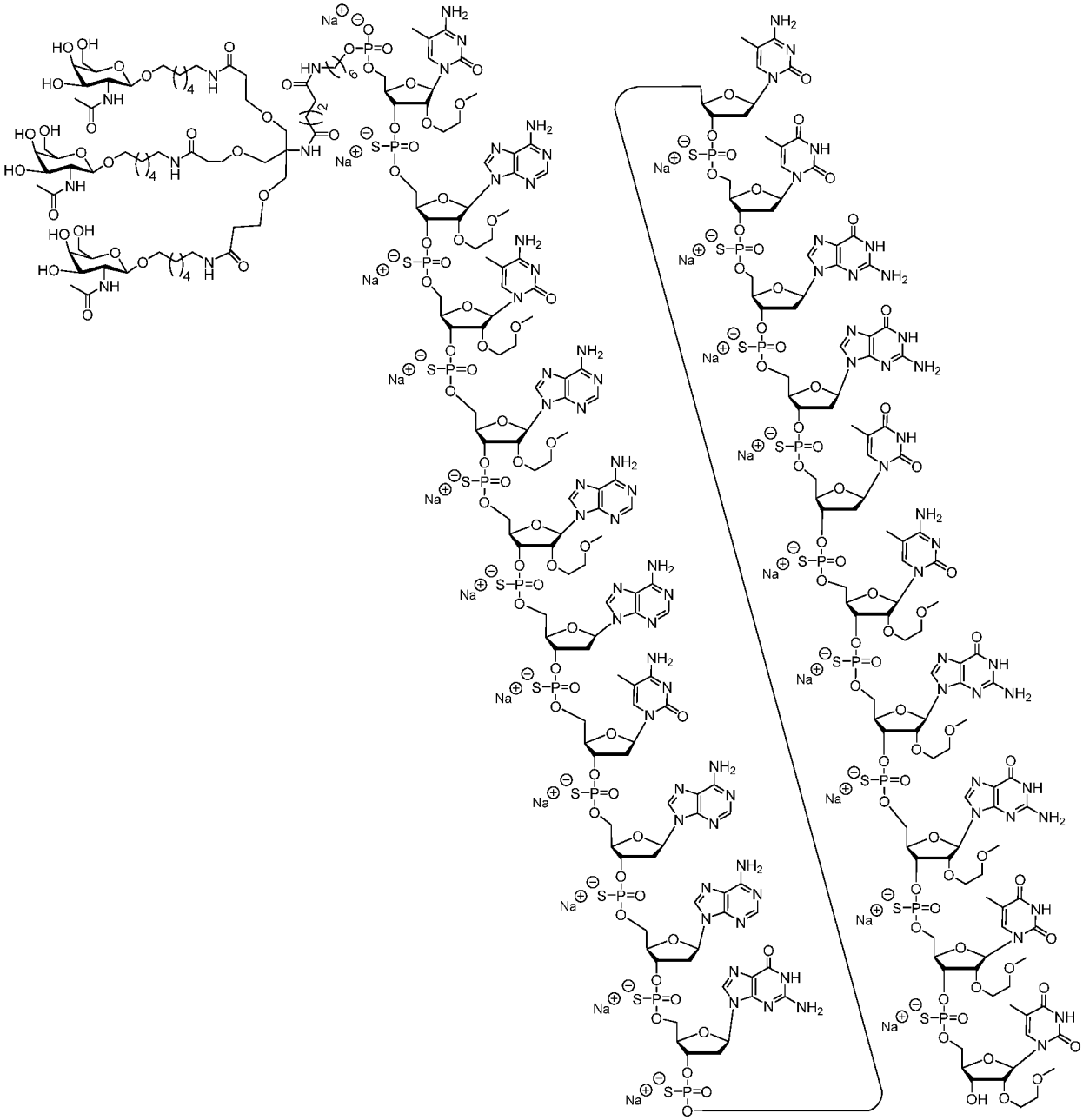


(SEQ ID NO: 3), or a salt thereof.

6. The method of claim 5, wherein the oligomeric compound is the sodium salt or the potassium salt.

7. A method of reducing AGT RNA or protein in a human subject having hypertension (HTN); resistant hypertension (RHTN); heart failure; chronic heart failure; heart failure with reduced ejection fraction (HFrEF); heart failure with preserved ejection fraction (HFpEF); diabetic nephropathy (DN); aortopathies associated with pathogenic TGF-β signaling; Marfan Syndrome; Loeys-Dietz Syndrome; Hereditary Hemorrhagic Telangiectasia; Familial Thoracic Aortic Aneurysm and Dissection; chronic kidney disease;

hepatic steatosis; or atherosclerosis comprising administering to the human subject a therapeutically effective amount of an oligomeric compound according to the following chemical structure:



(SEQ ID NO: 3).

8. A method of reducing AGT RNA or protein in a human subject having hypertension (HTN); resistant hypertension (RHTN); heart failure; chronic heart failure; heart failure with reduced ejection fraction (HFrEF); heart failure with preserved ejection fraction (HFpEF); diabetic nephropathy (DN); aortopathies associated with pathogenic TGF-β signaling; Marfan Syndrome; Loeys-Dietz Syndrome; Hereditary Hemorrhagic Telangiectasia; Familial Thoracic Aortic Aneurysm and Dissection; chronic kidney disease; hepatic steatosis; or atherosclerosis comprising administering to the human subject a therapeutically effective amount of an oligomeric compound comprising a modified oligonucleotide and a conjugate group according

to the following formula: $GalNAc_3$-$7_{a\text{-}o'}$ mCes Aes mCes Aes Aes Ads mCds Ads Ads Gds mCds Tds Gds Gds Tds mCes Ges Ges Tes Te (SEQ ID NO: 3); wherein,

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

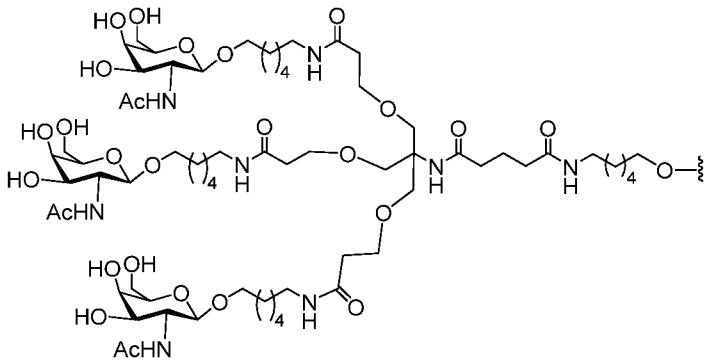
e = a 2'-MOE sugar moiety,

d = a 2'-β-D-deoxyribosyl sugar moiety,

s = a phosphorothioate internucleoside linkage,

o' = 5'-P(OH)(=O)-O-3', and

$GalNAc_3$-7_a =



9. The method of any one of claims 1-8, wherein the therapeutically effective amount is 25 mg.

10. The method of any one of claims 1-8, wherein the therapeutically effective amount is 40 mg.

11. The method of any one of claims 1-8, wherein the therapeutically effective amount is 60 mg.

12. The method of any one of claims 1-8, wherein the therapeutically effective amount is 80 mg.

13. The method of any one of claims 1-8, wherein the therapeutically effective amount is 120 mg.

14. The method of any one of claims 1-8, wherein the therapeutically effective amount is about 25 mg.

15. The method of any one of claims 1-8, wherein the therapeutically effective amount is about 40 mg.

16. The method of any one of claims 1-8, wherein the therapeutically effective amount is about 60 mg.

17. The method of any one of claims 1-8, wherein the therapeutically effective amount is about 80 mg.

18. The method of any one of claims 1-8, wherein the therapeutically effective amount is about 120 mg.

19. The method of any one of claims 1-8, wherein the therapeutically effective amount is any of 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, or 200 mg.

20. The method of any one of claims 1-8, wherein the therapeutically effective amount is any of 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, or about 200 mg.

21. The method of any one of claims 1-8, wherein the therapeutically effective amount is within the range of any of 25 mg to 200 mg, 30 mg to 200 mg, 40 mg to 200 mg, 60 mg to 200 mg, 80 mg to 200 mg, 100 mg to 200 mg, 120 mg to 200 mg, 150 mg to 200 mg, 25 mg to 120 mg, 30 mg to 120 mg, 40 mg to 120 mg, 60 mg to 120 mg, 80 mg to 120 mg, 40 mg to 80 mg, or 60 mg to 80 mg.

22. The method of any one of claims 1-8, wherein the therapeutically effective amount is any of 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, or less than 30 mg.

23. The method of any one of claims 1-8, wherein the therapeutically effective amount is any of 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, or less than about 30 mg.

24. The method of any one of claims 1-8, wherein the therapeutically effective amount is any of 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, at least 150 mg, at least 155 mg, at least 160 mg, at least

165 mg, at least 170 mg, at least 175 mg, at least 180 mg, at least 185, at least 190 mg, at least 195 mg, and at least 200 mg.

25. The method of any one of claims 1-8, wherein the therapeutically effective amount is any of 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, at least about 155 mg, at least about 160 mg, at least about 165 mg, at least about 170 mg, at least about 175 mg, at least about 180 mg, at least about 185, at least about 190 mg, at least about 195 mg, and at least about 200 mg.

26. The method of any one of claims 1-8, wherein the therapeutically effective amount is about 80 mg to about 120 mg.

27. The method of any one of claims 1-26, comprising administering the oligomeric compound once every week.

28. The method of any one of claims 1-26, comprising administering the oligomeric compound once every 2 weeks.

29. The method of any one of claims 1-26, comprising administering the oligomeric compound once every 3 weeks.

30. The method of any one of claims 1-26, comprising administering the oligomeric compound once every 4 weeks.

31. The method of any one of claims 1-26, comprising administering the oligomeric compound twice every week.

32. The method of any one of claims 1-26, comprising administering the oligomeric compound three times every week.

33. The method of any one of claims 1-26, comprising administering the oligomeric compound four times every week.

34. The method of any one of claims 1-26, comprising administering the oligomeric compound five times every week.

35. The method of any one of claims 1-26, comprising administering the oligomeric compound six times every week.

36. The method of any one of claims 1-26, comprising administering the oligomeric compound once every day, once every other day, once every 3 days, once every 4 days, once every 5 days, or once every 6 days.

37. The method of any one of claims 1-36, wherein at least one symptom of hypertension (HTN); resistant hypertension (RHTN); heart failure; chronic heart failure; heart failure with reduced ejection fraction

(HFrEF); heart failure with preserved ejection fraction (HFpEF); diabetic nephropathy (DN); aortopathies associated with pathogenic TGF-β signaling; Marfan Syndrome; Loeys-Dietz Syndrome; Hereditary Hemorrhagic Telangiectasia; Familial Thoracic Aortic Aneurysm and Dissection; chronic kidney disease; hepatic steatosis; or atherosclerosis is reduced or improved.

38. The method of any one of claims 1-36, wherein the human subject has hypertension or resistant hypertension and at least one symptom of hypertension or resistant hypertension is reduced or improved.

39. The method of claim 38, wherein at least one symptom is headaches, nosebleeds, fatigue, confusion, vision problems, chest pain, difficulty breathing, irregular heartbeat, blood in urine, or a combination thereof.

40. The method of claim 38 or 39, wherein administering the oligomeric compound reduces blood pressure (BP), reduces systolic blood pressure (SBP), reduces diastolic blood pressure (DBP), achieves <140/90 mmHg BP, achieves <130/80 mmHg BP, improves quality of life as assessed by patient reported outcomes, or any combination thereof.

41. The method of any one of claims 1-36, wherein the human subject has heart failure and at least one symptom of heart failure is reduced or improved.

42. The method of claim 41, wherein at least one symptom is a symptom due to fluid volume excess including dyspnea, orthopnea, edema, hepatic congestion, and ascites; a symptom due to a diminished cardiac output including fatigue, dizziness, and weakness; or a combination thereof.

43. The method of claim 41 or 42, wherein administering the oligomeric compound reduces rates of cardiovascular (CV) mortality, reduces heart failure hospitalization and urgent visits, reduces N-terminal prohormone B-type natriuretic peptide (NT-proBNP) levels, reduces B-type natriuretic peptide (BNP) levels, reduces cardiac troponin T (cTnT) levels, reduces high-sensitive cardiac troponin T (hs-cTnT) levels, improves cardiac function, reduces cardiac dilation, reduces cardiac fibrosis, increases or improves LVEF (left ventricular ejection fraction), reduces or improves LVESV (left ventricular end systolic volume), reduces or improves LVEDV (left ventricular end diastolic volume), increases or improves left ventricle (LV) strain, improves 6 minute walk test, improves quality of life, or any combination thereof.

44. The method of any one of claims 1-36, wherein the human subject has Marfan syndrome and at least one symptom of Marfan syndrome is reduced or improved.

45. The method of claim 44, wherein administering the oligomeric compound reduces or improves aortic root dilation, mortality, aortic root surgery, or any combination thereof.

46. The method of any one of claims 1-45, wherein the oligomeric compound is administered by subcutaneous injection.

47. The method of claim 46, wherein the oligomeric compound is administered by a syringe.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 22/27138

A. CLASSIFICATION OF SUBJECT MATTER
IPC - A61K 48/00; C07H 21/02; A61K 31/712 (2022.01)
CPC - A61K 31/7088; A61K 31/712; A61K 48/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2017/062816 A2 (IONIS PHARMACEUTICALS, INC.) 13 April 2017 (13.04.2017); pg. 2, ln 23-24, pg. 26, ln 1-3, 7, pg. 27, ln 11-18, 25, pg. 58, ln 22-28, pg. 59, ln 13-21	1-26
A	WO 2014/179629 A2 (ISIS PHARMACEUTICALS, INC.) 06 November 2014 (06.11.2014); entire document	1-26
A	US 2018/0273952 A1 (Ionis Pharmaceuticals, Inc.) 27 September 2018 (27.09.2018); entire document	1-26
A	US 2018/0251764 A1 (Roche Innovation Center Copenhagen A/S) 06 September 2018 (06.09.2018); entire document	1-26

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 July 2022	AUG 11 2022
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Kari Rodriquez Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 22/27138

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. ☒ forming part of the international application as filed:

      ☒ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 22/27138

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 27-47
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.