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(54) Title: METHODS AND COMPOSITIONS FOR REDUCING ANGIOTENSINOGEN

(57) Abstract: Provided herein are methods of reducing the amount of AGT RNA and/or AGT protein in a subject having or at risk for heart failure, such as heart failure with reduced ejection fraction (HFrEF), heart failure with mid-range ejection fraction (HFmrEF), or heart failure with preserved ejection fraction (HFpEF), and, in particular instances, a subject who is, or is at risk of being, intolerant to treatment with a renin-angiotensin-aldosterone system (RAAS) inhibitor. Also provided herein are methods for treating heart failure (such as HFrEF, HFmrEF or HFpEF). Methods provided herein include administering to a subject an oligomeric agent containing a modified oligonucleotide containing a nucleobase sequence complementary to a sequence in an AGT nucleic acid, such as ION904. Further provided herein are pharmaceutical compositions containing ION904.



METHODS AND COMPOSITIONS FOR REDUCING ANGIOTENSINOGEN

CROSS REFERENCE TO RELATED APPLICATION

[0001] This PCT application claims the benefit of U.S. provisional application no. 63/596,175, filed on November 3, 2023, the entire contents of which is hereby incorporated by reference in its entirety.

SEQUENCE LISTING

[0002] The present application is being filed concurrently with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled BIOL0479USLSEQ.xml, created on October 30, 2023, which is 47 KB in size. The contents of the electronic format of the sequence listing are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

[0003] Compositions and methods described herein relate to reducing the amount of angiotensinogen (AGT) in a cell or subject, for example a subject having or at risk for heart failure, such as heart failure with reduced ejection fraction (HFrEF). Compositions and methods also relate to methods for ameliorating symptoms of, and treating, heart failure, including HFrEF.

BACKGROUND

[0004] Heart failure (HF), a clinical syndrome becoming a global public health issue imposing serious burdens on healthcare systems, is characterized by significant mortality, frequent hospitalization, and poor quality of life (QOL), with an overall prevalence that is steadily increasing worldwide. (Shahim et al. (2023) *Cardiac Failure Review* 9:e11; Ambrosy et al., *Curr Heart Fail Rep* 2014; 11: 416-427; Heidenreich et al., *Circ Heart Fail* 2013; 6: 606-619). Symptoms of heart failure include, but are not limited to, fatigue, rapid or irregular heartbeat, palpitation, shortness of breath, chest pain, dizziness, weakness, dyspnea, orthopnea, edema, hepatic congestion, and ascites. HF can be stratified into three groups by assessment of left ventricular (LV) ejection fraction (EF) (i.e., a measure of how much blood is pumped from the left ventricle with each contraction): heart failure with reduced EF (HFrEF; also referred to as systolic HF), heart failure with mid-range EF

(HFmrEF) and heart failure with preserved EF (HFpEF; also referred to as diastolic HF) with each of the three groups having different demographics, comorbidities, and responses to therapies.

[0005] Approximately 40%-60% of HF patients are classified as HFrEF, (Shahim et al. (2023) *Cardiac Failure Review* 9:e11). HFrEF is associated with diminished contractility of the heart muscle and cardiovascular conditions that adversely impact left ventricular systolic function (e.g., coronary artery disease) and LV remodeling, and the most prevalent cause of HFrEF is ischemic heart disease. Four classes of medications, known as the “four pillars” of heart failure therapy, greatly improve outcome, morbidity and mortality and attenuate adverse cardiac remodeling in patients with HFrEF, though only for those who can tolerate them at guideline- recommended target doses. See, e.g., Heidenreich et al (2022) *Circulation* 145(18):e895-e1032, 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Medicines in two of the four pillars inhibit the renin-angiotensin-aldosterone system (RAAS) (RAAS inhibitors), while others blunt the detrimental sympathetic nervous output to the heart (beta blockers) or antagonize sodium-glucose cotransporter-2 receptors (SGLT2) in the kidneys to act as a weak diuretic and attenuate adverse remodeling. Specific therapies are available and recommended for HFrEF, however, those treatments lack efficacy in treating HFpEF (see, e.g., Simmonds et al. (2020) *Cells* 9:242). ESC recently gave class I recommendation to SGLT2 inhibitors for HFmrEF and HFpEF for the first time at their 2023 congress.

[0006] Activation of the RAAS and the sympathetic nervous system (i.e., neurohormonal activation) occurs in response to decreases in cardiac output and renal perfusion as a compensatory homeostatic response to low cardiac output seen in heart failure. Neurohormonal activation is associated with a cascade of effects on the peripheral vasculature, heart and kidneys (see, e.g., Hartupée and Mann (2017) *Nat Rev Cardiol* 14(1): 30–38). The net effect of responses is to produce hemodynamic changes in heart, kidneys and vasculature to increase cardiac output and ventricular filling. The heart also compensates at the cellular level by increasing myocyte size to counteract the reduction in cardiac output, leading to cardiac hypertrophy and adverse remodeling at the organ level. While this compensatory remodeling is initially beneficial, the heart and individual myocytes eventually grow to a point that they can no longer support their own metabolic needs, and the heart eventually fails to produce enough cardiac output to perfuse vital organs and meet the metabolic demands of the body. This leads to end-stage heart failure and death will occur without heart transplantation.

[0007] Several classes of RAAS inhibitors have been developed over the last several decades and have demonstrated the ability to improve morbidity and mortality in heart failure and attenuate adverse cardiac remodeling described above. Classes of RAAS inhibitors developed for heart failure include: (i) angiotensin converting enzyme inhibitors (ACEi) that block the conversion of Ang I to Ang II, thereby reducing cardiac afterload or the force against which the heart must pump; (ii) angiotensin receptor blockers (ARBs) that competitively inhibit AT1 receptors and block action of Ang II at end organs which also results in reduction of cardiac afterload; (iii) mineralocorticoid receptor antagonists (MRA) competitively inhibit mineralocorticoid receptors in the distal convoluted tubules of the kidneys to block the action of aldosterone, thereby enhancing natriuresis and diuresis and reducing cardiac afterload; and (iv) the angiotensin receptor blocker-neprilysin inhibitor (ARNi), which combines the ARB valsartan with sacubitril, a neprilysin inhibitor (NI), a circulating endogenous peptidase that acts to breakdown B-type or brain natriuretic peptide (BNP), thereby potentiating the activity of BNP and enhancing natriuresis and diuresis to reduce cardiac preload and afterload. Despite overwhelming evidence of the benefits of RAAS inhibitors, there is abundant evidence that utilization and efficacy is far from universal, and when RAAS inhibitors are used they are rarely prescribed at guideline-recommended target doses due, in part, to side effects of these drugs.

[0008] For example, many patients have intolerances that limit use of ACEi, particularly at >50% of guideline-recommended target doses. For example, some patients experience persistent cough and/or angioedema, thought to be related to elevated bradykinin levels arising from ACE inhibition. Although first investigated as a possible alternative for HF patients who could not tolerate ACEi, ARB therapy has been associated with renal dysfunction and hyperkalemia in some HF patients. Furthermore, combining ACEi and ARBs can exacerbate renal dysfunction and cause difficult to control hyperkalemia, leading to underdosing and drug cessation, and this combination of ACEi and ARBs is considered contraindicated by European and American Cardiology societies. Treatment with MRA has been associated with hyperkalemia, renal dysfunction and gynecomastia in landmark heart failure trials. As a monotherapy, sacubitril failed to demonstrate efficacy in heart failure patients. Combinations of NI with ACEi resulted in cases of severe angioedema due to the combined effects of ACE and neprilysin inhibition on bradykinin levels. Because ARNi contains an ARB, it is associated with many of the same toxicities as ACEi and ARBs including hypotension, renal dysfunction, acute kidney injury (AKI) and hyperkalemia. Many contemporary registry studies

evaluating the real world utilization of GDMT have demonstrated that substantial proportions of HF patients are either never prescribed GDMT or they are prescribed GDMT at suboptimal doses that have not shown to have clinical benefit in landmark studies. These registries consistently show that patients who are not prescribed GDMT or who are prescribed <50% of guideline-directed target doses of ACEi, ARB, ARNi or MRA have significantly worse morbidity and mortality than those taking guideline-recommended target doses. Intolerance to RAAS inhibitors is further exacerbated when multiple classes of RAAS inhibitors (such as ARNI + MRA) are used concurrently or when these drugs are used in patients with baseline renal dysfunction or borderline renal function.

[0009] Currently, there are limited therapeutic options to fully inhibit the RAAS pathway in HF patients with intolerance to existing RAAS inhibitors so that they can achieve the desired clinical benefits of guideline target doses. Patients with severe renal dysfunction and hyperkalemia are unlikely to tolerate RAAS inhibitors let alone combination of ARNI and MRA at guideline-recommended target doses. American and European guidelines recommend combination of vasodilators isosorbide dinitrate and hydralazine as second line therapy for HF patients with renal dysfunction or other contraindications to ACE/ARB/ARNi. However, the pure vasodilators lack RAAS inhibitory activity and show no ability to attenuate adverse remodeling in direct head-to-head studies. Underprescription of RAAS inhibitors is still a global problem affecting nearly a majority of patients with heart failure. Though reasons for non-prescription and underdosing of RAAS inhibitors are multifactorial, intolerance is a major factor in limiting treatment of a substantial number of patients. Thus, effective therapies to treat HF patients, particularly HFrEF patients, who are unable, or at risk of being able, to tolerate Guideline-recommended doses of RAAS inhibitors remains a major unmet need.

SUMMARY OF THE INVENTION

[0010] Described herein are methods for reducing the amount of angiotensinogen (AGT) RNA and/or AGT protein in a subject. In certain embodiments, the subject is or is at risk of being intolerant to treatment with a renin-angiotensin-aldosterone system (RAAS) inhibitor. In certain embodiments, the subject has, or is at risk for, heart failure, e.g., heart failure with reduced ejection fraction (HFrEF). In certain embodiments, methods include administering about 15 mg to about 200 mg of an oligomeric agent having a modified oligonucleotide consisting of 16-30 linked nucleosides wherein the modified oligonucleotide comprises a nucleobase sequence of at least 16 contiguous

nucleosides at least 80% complementary to the nucleobase sequence of an equal length region of a nucleobase sequence of SEQ ID NO: 1 or SEQ ID NO: 2, or salt thereof, to a subject having or at risk for heart failure. In certain embodiments, the amount of AGT RNA and/or AGT protein in the subject is decreased by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent. In certain embodiments the subject has or is at risk for heart failure with reduced ejection fraction (HFrEF), heart failure with mid-range ejection fraction (HFmrEF), heart failure with improved ejection fraction (HFimpEF), or heart failure with preserved ejection fraction (HFpEF). Described herein are methods for reducing the amount of angiotensinogen (AGT) RNA and/or AGT protein in a subject who is or is at risk of being intolerant to treatment with a renin-angiotensin-aldosterone system (RAAS) inhibitor, comprising administering about 15 mg to about 200 mg of an oligomeric agent or salt thereof to a subject having or at risk for heart failure, wherein the oligomeric agent comprises a modified oligonucleotide consisting of 16-30 linked nucleosides, and wherein the modified oligonucleotide comprises a nucleobase sequence of at least 16 contiguous nucleosides at least 80% complementary to the nucleobase sequence of an equal length region of nucleobases 2046-2061 of SEQ ID NO: 1 or nucleobases 14940-14955 of SEQ ID NO: 2. In certain embodiments, the amount of AGT RNA and/or AGT protein in the subject is decreased by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent. In certain embodiments, the subject has or is at risk for, or the heart failure is, heart failure with reduced ejection fraction (HFrEF), heart failure with mid-range ejection fraction (HFmrEF), heart failure with improved ejection fraction (HFimpEF), or heart failure with preserved ejection fraction (HFpEF). Described are methods for reducing the amount of AGT RNA and/or AGT protein in a subject intolerant, or at risk of being intolerant, to treatment with a renin-angiotensin-aldosterone system (RAAS) inhibitor, comprising administering an oligomeric compound or salt thereof to a subject having or at risk for heart failure; wherein the subject is intolerant, or is at risk of being intolerant, to treatment with a RAAS inhibitor; and wherein the amount of AGT protein in the subject is reduced by at least 70%, at least 75%, at least 80% or at least 85% but less than 95% in the subject, wherein the oligomeric compound is a GalNAc-conjugated modified oligonucleotide, wherein the modified oligonucleotide is represented by the following chemical notation (5' to 3'):

${}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 4) or a salt thereof; wherein

A = an adenine nucleobase, ${}^m\text{C}$ = a 5-methyl cytosine nucleobase, G = a guanine nucleobase, T = a thymine nucleobase, e = a 2'-MOE sugar moiety, k = a cEt sugar moiety, d = an unmodified DNA sugar moiety, s = a phosphorothioate internucleoside linkage, and o = a phosphodiester internucleoside linkage;

and wherein

GalNAc is an N-acetyl galactosamine conjugate moiety.

[0011] Described are methods of treating heart failure in a subject having or at risk for heart failure who is or is at risk of being intolerant to treatment with a renin-angiotensin-aldosterone system (RAAS) inhibitor, comprising administering about 15 mg to about 200 mg of an oligomeric agent having a modified oligonucleotide consisting of 16-30 linked nucleosides wherein the modified oligonucleotide comprises a nucleobase sequence of at least 16 contiguous nucleosides at least 80% complementary to a nucleobase sequence of an equal length region of SEQ ID NO: 1 or SEQ ID NO: 2, or salt thereof, to a subject having or at risk for heart failure. In certain embodiments the amount of AGT RNA and/or AGT protein in the subject is decreased by at least 70%, at least 75%, at least 80%, or at least 85% and less than 95% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent. In certain embodiments the subject has or is at risk for heart failure with reduced ejection fraction (HFrEF), heart failure with mid-range ejection fraction (HFmrEF), heart failure with improved ejection fraction (HFimpEF), or heart failure with preserved ejection fraction (HFpEF). Described are methods of treating heart failure in a subject having or at risk for heart failure who is intolerant or who is at risk of being intolerant to treatment with a renin-angiotensin-aldosterone system (RAAS) inhibitor, comprising administering about 15 mg to about 200 mg of an oligomeric agent or salt thereof to a subject having or at risk for heart failure, wherein the oligomeric agent comprises a modified oligonucleotide consisting of 16-30 linked nucleosides, and wherein the modified oligonucleotide comprises a nucleobase sequence of at least 16 contiguous nucleosides at least 80% complementary to the nucleobase sequence of an equal length region of nucleobases 2046-2061 of SEQ ID NO: 1 or nucleobases 14940-14955 of SEQ ID NO: 2. In certain embodiments the amount of AGT RNA and/or AGT protein in the subject is decreased by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent. In certain embodiments,

the subject has or is at risk for, or the heart failure is, heart failure with reduced ejection fraction (HFrEF), heart failure with mid-range ejection fraction (HFmrEF), heart failure with improved ejection fraction (HFimpEF), or heart failure with preserved ejection fraction (HFpEF). Described are methods of treating heart failure in a subject, comprising administering an oligomeric compound or a salt thereof to a subject having or at risk of having heart failure, wherein the subject is or is at risk of being intolerant to treatment with a RAAS inhibitor; wherein treatment results in one or more symptoms ameliorated and/or lack of progression of heart failure, wherein the oligomeric compound is a GalNAc-conjugated modified oligonucleotide, wherein the modified oligonucleotide is represented by the following chemical notation (5' to 3'):

${}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 4) or a salt thereof; wherein

A = an adenine nucleobase, ${}^m\text{C}$ = a 5-methyl cytosine nucleobase, G = a guanine nucleobase, T = a thymine nucleobase, e = a 2'-MOE sugar moiety, k = a cEt sugar moiety, d = an unmodified DNA sugar moiety, s = a phosphorothioate internucleoside linkage, and o = a phosphodiester internucleoside linkage; and wherein

GalNAc is an N-acetyl galactosamine conjugate moiety.

[0012] Additionally described are methods of treating heart failure in a subject, comprising administering about 50 mg to about 200 mg an oligomeric compound or a salt thereof to a subject; wherein administering oligomeric compound results in amelioration of one or more symptoms and/or lack of progression of heart failure, wherein the oligomeric compound is a GalNAc-conjugated modified oligonucleotide, wherein the modified oligonucleotide is represented by the following chemical notation (5' to 3'): ${}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 4) or a salt thereof; wherein

A = an adenine nucleobase, ${}^m\text{C}$ = a 5-methyl cytosine nucleobase, G = a guanine nucleobase, T = a thymine nucleobase, e = a 2'-MOE sugar moiety, k = a cEt sugar moiety, d = an unmodified DNA sugar moiety, s = a phosphorothioate internucleoside linkage, and o = a phosphodiester internucleoside linkage; and wherein

GalNAc is an N-acetyl galactosamine conjugate moiety.

[0013] Also described are uses of an oligomeric agent or salt thereof for treating heart failure in a subject having or at risk for heart failure who is or is at risk of being intolerant to treatment with a renin-angiotensin-aldosterone system (RAAS) inhibitor, wherein the oligomeric agent has a modified oligonucleotide consisting of 16-30 linked nucleosides and wherein the modified

oligonucleotide comprises a nucleobase sequence of at least 16 contiguous nucleosides at least 80% complementary to the nucleobase sequence of an equal length region of SEQ ID NO: 1 or SEQ ID NO: 2, and the subject has or is at risk for heart failure. In certain embodiments the oligomeric agent decreases the amount of AGT RNA and/or AGT protein in a subject by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent; and in certain embodiments the subject has or is at risk for heart failure with reduced ejection fraction (HFrEF), heart failure with mid-range ejection fraction (HFmrEF), heart failure with improved ejection fraction (HFimpEF), or heart failure with preserved ejection fraction (HFpEF). Described are uses of an oligomeric agent or salt thereof for treating heart failure in a subject having or at risk for heart failure who is or is at risk of being intolerant to treatment with a renin-angiotensin-aldosterone system (RAAS) inhibitor, wherein the oligomeric agent comprises a modified oligonucleotide consisting of 16-30 linked nucleosides and wherein the modified oligonucleotide comprises a nucleobase sequence of at least 16 contiguous nucleosides at least 80% complementary to the nucleobase sequence of an equal length region of nucleobases 2046-2061 of SEQ ID NO: 1 or nucleobases 14940-14955 of SEQ ID NO: 2, or salt thereof and the subject has or is at risk for heart failure. In certain embodiments the oligomeric agent decreases the amount of AGT RNA and/or AGT protein in a subject by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent. In certain embodiments the subject has or is at risk for heart failure with reduced ejection fraction (HFrEF), heart failure with mid-range ejection fraction (HFmrEF), heart failure with improved ejection fraction (HFimpEF), or heart failure with preserved ejection fraction (HFpEF). Also described are uses of an oligomeric compound or a salt thereof for treating heart failure in a subject intolerant to, or at risk of being intolerant to, treatment with a RAAS inhibitor, wherein: the subject does not progress or one or more symptoms are ameliorated; wherein the oligomeric compound is a GalNAc-conjugated modified oligonucleotide, wherein the modified oligonucleotide is represented by the following chemical notation (5' to 3'):

${}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 4) or a salt thereof; wherein

A = an adenine nucleobase, ${}^m\text{C}$ = a 5-methyl cytosine nucleobase, G = a guanine nucleobase, T = a thymine nucleobase, e = a 2'-MOE sugar moiety, k = a cEt sugar moiety, d = an unmodified DNA sugar moiety, s = a phosphorothioate internucleoside linkage, and o = a phosphodiester

internucleoside linkage; and wherein

GalNAc is an N-acetyl galactosamine conjugate moiety.

[0014] Described are uses of 50 mg to 200 mg of an oligomeric compound or a salt thereof for treating heart failure in a subject having or at risk for heart failure; wherein the oligomeric compound is a GalNAc-conjugated modified oligonucleotide, wherein the modified oligonucleotide is represented by the following chemical notation (5' to 3'):

${}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 4) or a salt thereof; wherein

A = an adenine nucleobase, ${}^m\text{C}$ = a 5-methyl cytosine nucleobase, G = a guanine nucleobase, T = a thymine nucleobase, e = a 2'-MOE sugar moiety, k = a cEt sugar moiety, d = an unmodified DNA sugar moiety, s = a phosphorothioate internucleoside linkage, and o = a phosphodiester internucleoside linkage; and wherein

GalNAc is an N-acetyl galactosamine conjugate moiety.

[0015] Also provided are uses of an oligomeric compound or a salt thereof for reducing the amount of AGT RNA and/or AGT protein in a subject intolerant, or at risk of being intolerant, to treatment with a renin-angiotensin-aldosterone system (RAAS) inhibitor, wherein the oligomeric compound is a GalNAc-conjugated modified oligonucleotide, wherein the modified oligonucleotide is represented by the following chemical notation (5' to 3'):

${}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 4) or a salt thereof; wherein

A = an adenine nucleobase, ${}^m\text{C}$ = a 5-methyl cytosine nucleobase, G = a guanine nucleobase, T = a thymine nucleobase, e = a 2'-MOE sugar moiety, k = a cEt sugar moiety, d = an unmodified DNA sugar moiety, s = a phosphorothioate internucleoside linkage, and o = a phosphodiester internucleoside linkage; and wherein

GalNAc is an N-acetyl galactosamine conjugate moiety; and wherein the oligomeric compound decreases to the amount of AGT RNA and/or AGT protein in a subject by at least 70%, at least 75%, at least 80% or at least 85% but less than 95% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent or salt thereof.

[0016] In certain embodiments, use is in a subject having or who is at risk for heart failure, selected from heart failure with reduced ejection fraction (HFrEF), heart failure with mid-range ejection fraction (HFmrEF), heart failure with improved ejection fraction (HFimPEF), or heart failure with preserved ejection fraction (HFpEF).

[0017] Also described herein are uses of an oligomeric agent or salt thereof in the manufacture of a medicament for reducing the amount of AGT RNA and/or AGT protein in a subject or for treating heart failure and/or ameliorating one or more symptoms of heart failure, wherein the oligomeric agent is a modified oligonucleotide consisting of 16-50 linked nucleosides, wherein the modified oligonucleotide has at least 16 contiguous nucleosides at least 80% complementary to the nucleobase sequence of an equal length region of SEQ ID NO: 1 or SEQ ID NO: 2. In certain embodiments the oligomeric agent decreases the amount of AGT RNA and/or AGT protein in a subject by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent or salt thereof; and wherein the subject has or is at risk for heart failure with reduced ejection fraction (HFrEF), heart failure with mid-range ejection fraction (HFmrEF), heart failure with improved ejection fraction (HFimpEF), or heart failure with preserved ejection fraction (HFpEF). Described are uses of an oligomeric agent or salt thereof in the manufacture of a medicament for reducing the amount of AGT RNA and/or AGT protein in a subject or for treating heart failure and/or ameliorating one or more symptoms of heart failure, wherein the oligomeric agent comprises a modified oligonucleotide consisting of 16-50 linked nucleosides, wherein the modified oligonucleotide comprises a nucleobase sequence comprising at least 13, or at least 16, contiguous nucleosides at least 80% complementary to the nucleobase sequence of an equal length region of nucleobases 2046-2061 of SEQ ID NO: 1 or nucleobases 14940-14955 of SEQ ID NO: 2. In certain embodiments the oligomeric agent decreases the amount of AGT RNA and/or AGT protein in a subject by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent or salt thereof. In certain embodiments, the subject has or is at risk for, or the heart failure is, heart failure with reduced ejection fraction (HFrEF), heart failure with mid-range ejection fraction (HFmrEF), heart failure with improved ejection fraction (HFimpEF), or heart failure with preserved ejection fraction (HFpEF).

[0018] Additionally described are unit doses useful in the provided methods. Described are unit doses comprising 50 mg to 200 mg of an oligomeric compound comprising a GalNAc-conjugated modified oligonucleotide represented by the following chemical notation (5' to 3'):

${}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 4) or a salt thereof; wherein

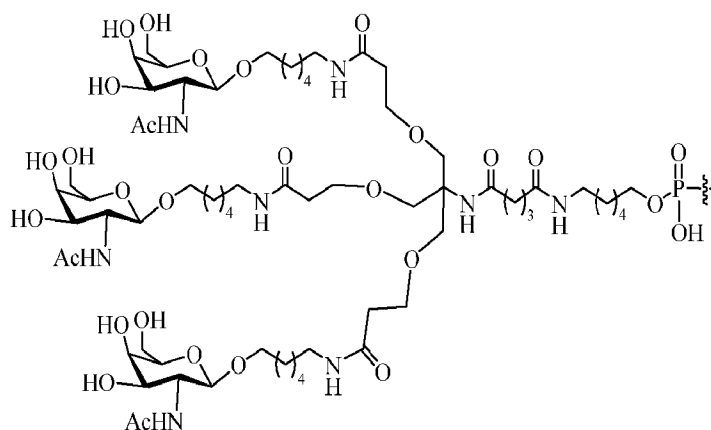
A = an adenine nucleobase, ${}^m\text{C}$ = a 5-methyl cytosine nucleobase, G = a guanine nucleobase,

T = a thymine nucleobase, e = a 2'-MOE sugar moiety, k = a cEt sugar moiety, d = an unmodified DNA sugar moiety, s = a phosphorothioate internucleoside linkage, and o = a phosphodiester internucleoside linkage; and wherein

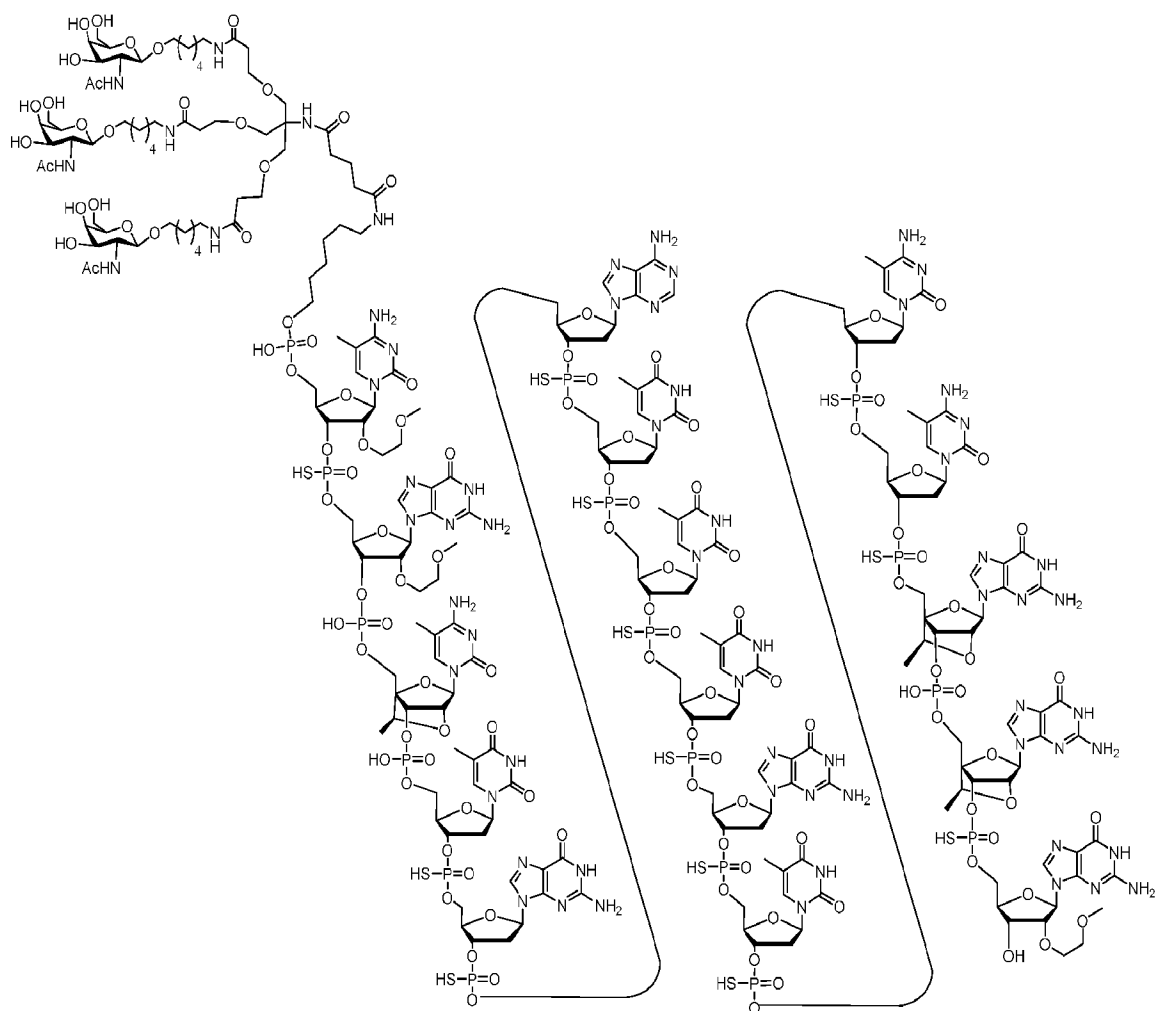
GalNAc is an N-acetyl galactosamine conjugate moiety.

[0019] Also described are unit doses comprising 50 mg to 150 mg of an oligomeric compound represented by the following chemical notation (5' to 3'): THA-C6-GalNAc₃-

^mC_{es}G_{eo}^mC_{ko}T_{ds}G_{ds}A_{ds}T_{ds}T_{ds}T_{ds}G_{ds}T_{ds}^mC_{ds}^mC_{ds}G_{ko}G_{ks}G_e (SEQ ID NO: 5) or a salt thereof; 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, k = a cEt sugar moiety, d = an unmodified DNA sugar moiety, s = a phosphorothioate internucleoside linkage, and o = a phosphodiester internucleoside linkage, and THA-C6-GalNAc₃=



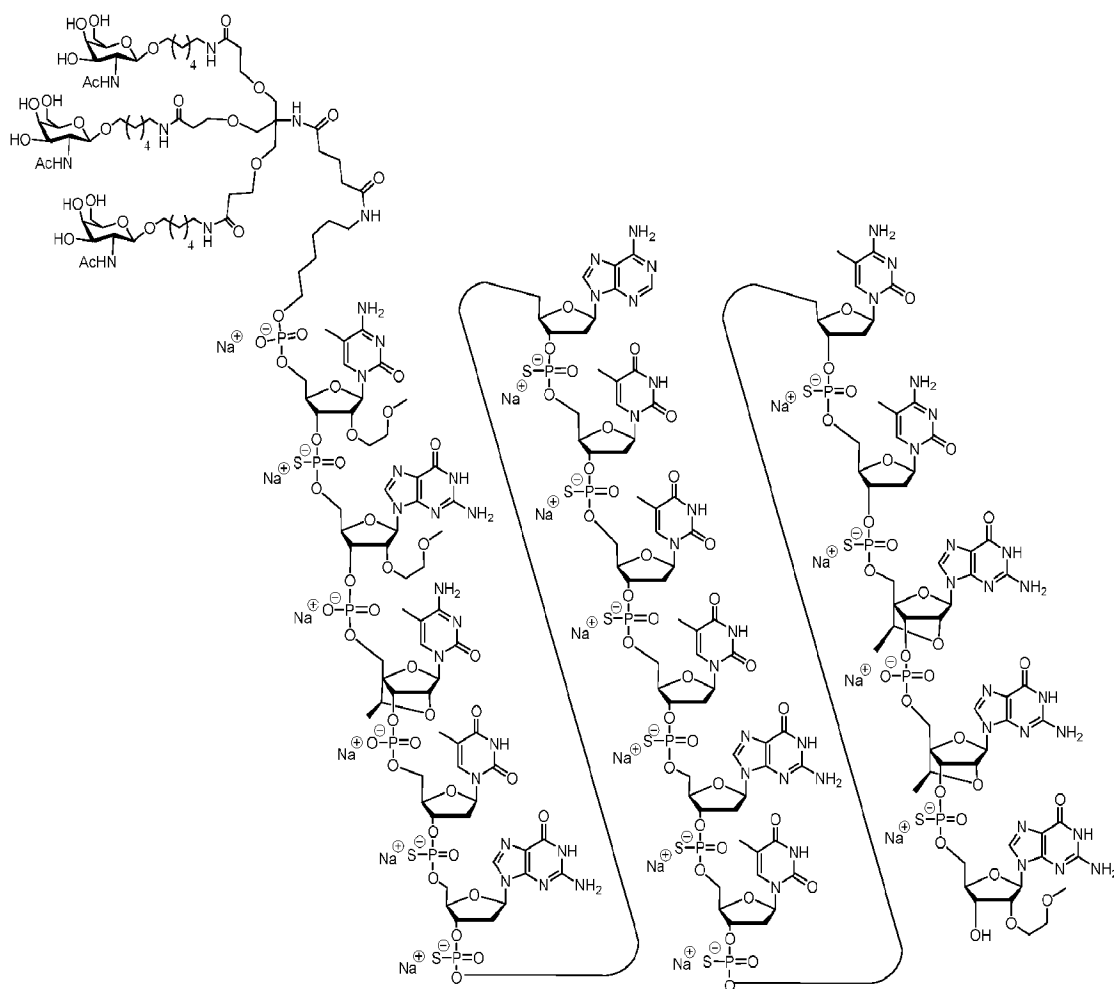
[0020] Also described are unit doses comprising 50 mg to 150 mg of an oligomeric compound represented by the following Structure 1:



(SEQ ID NO: 5),

or a salt thereof.

[0021] Also described are unit doses comprising 50 mg to 150 mg an oligomeric compound represented by the following sodium salt Structure 2:



(SEQ ID NO: 5).

[0022] Unit doses described comprise an amount of oligomeric compound or salt thereof within the range of about 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 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 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 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 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 150 mg, 100 mg to 140 mg, 100 mg to 120 mg, 100 mg to 110 mg, 110 mg to 150 mg, 110 mg to 140 mg, 110 mg to 130 mg, 110 mg to 120 mg, 120 mg to 150 mg, 120 mg to 140 mg, 120 mg to 130 mg, 130 mg to 150 mg, 130 mg to 140 mg, 140 mg to 150 mg, 55 mg to 125 mg, 55 mg to 115 mg, 55 mg to 105 mg, 55 mg to 95 mg, 55 mg to 85 mg, 55 mg to 75 mg, 55 mg to 65 mg, 65 mg to 125 mg, 65 mg to 115 mg, 65 mg to 105 mg, or 65 mg to 95 mg, 65 mg to 85 mg, 65 mg to 75 mg, 75 mg to 125 mg, 75 mg to 115 mg, 75 mg to 105 mg, 75 mg to 95 mg, 75 mg to 85 mg, 85 mg

to 125 mg, 85 mg to 115 mg, 85 mg to 105 mg, or 85 mg to 95 mg. Unit doses described comprise an amount of oligomeric compound or salt thereof within the range of about 50 mg to about 150 mg, about 50 mg to about 140 mg, about 50 mg to about 120 mg, about 50 mg to about 110 mg, about 50 mg to about 100 mg, about 50 mg to about 80 mg, about 50 mg to about 70 mg, about 50 mg to about 60 mg, about 60 mg to about 150 mg, about 60 mg to about 140 mg, about 60 mg to about 120 mg, about 60 mg to about 110 mg, about 60 mg to about 100 mg, about 60 mg to about 80 mg, about 60 mg to about 70 mg, about 70 mg to about 150 mg, about 70 mg to about 140 mg, about 70 mg to about 120 mg, about 70 mg to about 110 mg, about 70 mg to about 100 mg, about 70 mg to about 80 mg, about 80 mg to about 150 mg, about 80 mg to about 140 mg, about 80 mg to about 120 mg, about 80 mg to about 110 mg, about 80 mg to about 100 mg, about 80 mg to about 90 mg, about 90 mg to about 150 mg, about 90 mg to about 140 mg, about 90 mg to about 120 mg, about 90 mg to about 110 mg, about 90 mg to about 100 mg, about 100 mg to about 150 mg, about 100 mg to about 140 mg, about 100 mg to about 120 mg, about 100 mg to about 110 mg, about 110 mg to about 150 mg, about 110 mg to about 140 mg, about 110 mg to about 130 mg, about 110 mg to about 120 mg, about 120 mg to about 150 mg, about 120 mg to about 140 mg, about 120 mg to about 130 mg, about 130 mg to about 150 mg, about 130 mg to about 140 mg, about 140 mg to about 150 mg, about 55 mg to about 125 mg, about 55 mg to about 115 mg, about 55 mg to about 105 mg, about 55 mg to about 95 mg, about 55 mg to about 85 mg, about 55 mg to about 75 mg, about 55 mg to about 65 mg, about 65 mg to about 125 mg, about 65 mg to about 115 mg, about 65 mg to about 105 mg, or about 65 mg to about 95 mg, about 65 mg to about 85 mg, about 65 mg to about 75 mg, about 75 mg to about 125 mg, about 75 mg to about 115 mg, about 75 mg to about 105 mg, about 75 mg to about 95 mg, about 75 mg to about 85 mg, about 85 mg to about 125 mg, about 85 mg to about 115 mg, about 85 mg to about 105 mg, or about 85 mg to about 95 mg. Unit doses are formulated as pharmaceutical compositions comprising a pharmaceutically acceptable carrier, adjuvant or excipient. Certain compositions comprise an oligomeric agent or salt thereof and a pharmaceutically acceptable carrier or excipient. Certain compositions comprise a pharmaceutically acceptable carrier or excipient which is sterile water or sterile saline or phosphate buffered saline. Certain compositions are formulated for parenteral administration. Certain compositions are formulated for subcutaneous, intramuscular, or intravenous administration. Described unit doses and compositions are useful in the methods and uses described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] Each of the following figures is provided by way of example and is not intended to limit the scope of the claimed invention.

[0024] FIG. 1 depicts results of reduction of AGT protein levels as compared to placebo following subcutaneous administration of a single dose of ION904.

[0025] FIG. 2 depicts results of mean plasma concentrations of ION904 versus time (24-hour profile) by dose following subcutaneous administration (linear scale).

[0026] FIG. 3 depicts results of mean plasma concentrations of ION904 versus time (24-hour profile) by dose following subcutaneous administration (semilogarithmic scale).

[0027] FIG. 4 depicts an inhibitory effect $E_{\max}$ model of plasma AGT (% of baseline) as a function of plasma concentrations of ION904 measured on day 29 of a study according to Example 2 following a single subcutaneous dose administration of ION904.

[0028] FIG. 5 depicts mean percent change from baseline of plasma AGT protein levels as compared to placebo following subcutaneous administration of monthly doses of ION904.

[0029] FIG. 6 depicts median percent change from baseline of plasma AGT protein levels as compared to placebo following subcutaneous administration of monthly doses of ION904.

[0030] FIG. 7 depicts a waterfall plot of individual subject percent change from baseline of plasma AGT protein levels and systolic blood pressure (SBP) change from baseline at day 99 of a study according to Example 3.

[0031] FIG. 8 depicts results of mean change from baseline in seated automated office SBP over time following subcutaneous administration of monthly doses of ION904.

[0032] FIG. 9 depicts results of mean change from baseline in seated automated office diastolic blood pressure (DBP) over time following subcutaneous administration of monthly doses of ION904.

DETAILED DESCRIPTION

[0033] 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. 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.

[0034] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[0035] I. DEFINITIONS

[0036] The following definitions are provided, along with additional definitions throughout the specification, for a complete understanding of the instant invention. Unless specific definitions are provided, nomenclature used in connection with, and 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. Unless otherwise indicated, the following terms have the following meanings.

[0037] As used herein, “2'-deoxynucleoside” means a nucleoside comprising a 2'-deoxyfuranosyl sugar moiety. Unless otherwise indicated, a 2'-deoxynucleoside is a 2'-β-D-deoxynucleoside which comprises a 2'-β-D-deoxyribosyl sugar moiety, which is in the β-D configuration in naturally occurring deoxyribonucleic acid (DNA). A 2'-deoxynucleoside or a nucleoside comprising an unmodified 2'-deoxyribosyl sugar moiety may be abasic, comprise a modified nucleobase, or may comprise an RNA nucleobase (uracil).

[0038] As used herein, “2'-deoxy sugar moiety” means a 2'-H(H) deoxyfuranosyl sugar moiety. Unless otherwise indicated, a 2'-deoxy sugar moiety is a 2'-β-D-deoxyribosyl sugar moiety, which has the β-D ribosyl configuration in naturally occurring deoxyribonucleic acid (DNA).

[0039] As used herein, “2'-MOE” means a 2'-OCH₂CH₂OCH₃ group at the 2'-position of a furanosyl sugar moiety. A “2'-MOE sugar moiety” means a sugar moiety with a 2'-OCH₂CH₂OCH₃ group at the 2'-position of a furanosyl sugar moiety. Unless otherwise indicated, a 2'-MOE sugar moiety is in the β-D-ribosyl stereochemical configuration. “MOE” means O-methoxyethyl.

[0040] As used herein, “2'-MOE nucleoside” or “2'-OCH₂CH₂OCH₃ nucleoside” means a nucleoside comprising a 2'-MOE sugar moiety (or 2'-OCH₂CH₂OCH₃ furanosyl sugar moiety).

[0041] As used herein, “2'-OMe” means a 2'-OCH₃ group at the 2'-position of a furanosyl sugar moiety. A “2'-OMe sugar moiety” means a sugar moiety with a 2'-OCH₃ group at the 2'-position of a furanosyl sugar moiety. Unless otherwise indicated, a 2'-OMe sugar moiety is in the β-D-ribosyl stereochemical configuration.

[0042] As used herein, “2'-OMe nucleoside” means a nucleoside comprising a 2'-OMe sugar moiety.

[0043] As used herein, “2'-F” means a 2'-fluoro group at the 2'-position of a furanosyl sugar moiety. A “2'-F sugar moiety” means a sugar moiety with a 2'-F group at the 2'-position of a furanosyl sugar moiety. Unless otherwise indicated, a 2'-F sugar moiety is in the β -D-ribose configuration.

[0044] As used herein, “2'-F nucleoside” means a nucleoside comprising a 2'-F sugar moiety.

[0045] As used herein “2'-NMA” means a 2'-OCH₂C(=O)-N(H)CH₃ group at the 2'-position of a furanosyl sugar moiety. A “2'-NMA sugar moiety” means a sugar moiety with a 2'-OCH₂C(=O)-N(H)CH₃ group at the 2'-position of a furanosyl sugar moiety.

[0046] As used herein, “2'-NMA nucleoside” means a nucleoside comprising a 2'-NMA sugar moiety.

[0047] As used herein, “2'-substituted nucleoside” means a modified nucleoside comprising a 2'-substituted furanosyl sugar moiety. 2'-substituted nucleosides include, but are not limited to, e.g., a 2'-OMe nucleoside, a 2'-MOE nucleoside, a 2'-F nucleoside, a 2'-NMA nucleoside, a cEt nucleoside, a LNA nucleoside.

[0048] As used herein, “2'-substitution” or “2'-substituted sugar moiety” means a modified furanosyl sugar moiety wherein the 2'-position is attached to at least one substituent other than H or OH. A 2'-substituted sugar moiety includes a bicyclic sugar moiety wherein the second ring is joined to the furanosyl ring at the 2'-position. 2'-substituted sugar moieties include, but are not limited to, 2'-OMe sugar moieties, 2'-MOE sugar moieties, 2'-F sugar moieties, 2'-NMA sugar moieties, cEt sugar moieties, and LNA sugar moieties.

[0049] 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.

[0050] As used herein, “abasic nucleoside” means a modified nucleoside in which the sugar moiety is not attached to a nucleobase.

[0051] As used herein, “about” means plus or minus 7% of the provided value.

[0052] As used herein, “active agent” refers to a composition or compound that has measurable specified activity when administered to a subject. An active agent may be, for example, an oligomeric agent, e.g., an antisense oligonucleotide. In certain embodiments an active agent is other than an oligomeric agent or an antisense oligonucleotide.

[0053] As used herein, “ameliorate” with reference to a symptom of a disease, disorder or condition means improvement in, or lessening of, at least one symptom of a disease, disorder or condition. Amelioration may be reduction in severity or frequency of a symptom or the delayed onset, or slowing of progression in the severity or frequency of, a symptom. Progression, frequency, or severity indicators may be determined by subjective or objective measures known in the art and/or described herein.

[0054] As used herein, “antisense activity” means any detectable and/or measurable change attributable (whether directly and/or indirectly) to hybridization of an antisense oligonucleotide to a target nucleic acid. For example, compounds have antisense activity when they alter the amount or activity of a target nucleic acid by 25% or more in an *in vitro* assay; or, for example compounds have antisense activity when they alter the amount or activity of a target nucleic acid by 25% or more in an *in vivo* assay. Antisense activity may be assessed in a standard assay. Herein, antisense activity is a decrease in the amount or expression of a target nucleic acid, e.g., a target RNA, or a protein encoded by such target nucleic acid compared to target nucleic acid levels or target protein levels in the absence of the oligonucleotide.

[0055] As used herein, “antisense agent” means an oligomeric agent comprising an antisense oligonucleotide.

[0056] As used herein, “antisense oligonucleotide” means an oligonucleotide having at least one nucleobase sequence that is complementary to a target nucleic acid (e.g., a nucleobase sequence of a target nucleic acid). An antisense oligonucleotide may be paired with a second oligonucleotide (herein, a “sense oligonucleotide”) that is complementary to the antisense oligonucleotide (for example, forming an “oligomeric duplex”), may be an unpaired antisense oligonucleotide (herein, a single-stranded antisense oligonucleotide), or may be a “hairpin oligonucleotide” that has at least one region that is self-complementary.

[0057] As used herein, “bicyclic sugar” or “bicyclic sugar moiety” means a modified sugar moiety comprising a furanosyl sugar moiety and a second ring, wherein the second ring is formed via a bridge connecting two non-geminal atoms in the ring of the furanosyl sugar moiety, thereby forming a bicyclic structure. Examples of bicyclic sugar moieties include locked nucleic acid (LNA) sugar moieties and constrained ethyl (cEt) sugar moieties as defined herein.

[0058] As used herein, “bicyclic nucleoside” or “BNA” means a nucleoside comprising a bicyclic sugar moiety.

[0059] As used herein, “cell-targeting moiety” means a conjugate moiety or portion of a conjugate moiety that has affinity for a particular cell type or particular cell types. For example, a cell-targeting moiety may have affinity for a cell surface moiety, such as a cell surface receptor on a particular cell type.

[0060] As used herein, “cleavable moiety” means a group of atoms comprising at least one bond that is cleaved under physiological conditions, e.g., in a cell, in a subject, such as a cleavable moiety cleaved inside a cell or sub-cellular compartment, e.g., an endosome or lysosome. In certain embodiments, a cleavable moiety may be cleaved by endogenous enzymes, such as nucleases, or under certain conditions, e.g., a certain pH.

[0061] As used herein, “complementary nucleobase(s)” or “complementary” in reference to a nucleobase(s) means nucleobases that form hydrogen bonds with one another. Complementary nucleobase pairs include, but are not limited to, adenine (A) and thymine (T), adenine (A) and uracil (U), cytosine (C) and guanine (G), 5-methylcytosine (^mC) and guanine (G). Certain modified nucleobases that are complementary to unmodified nucleobases or to other modified nucleobases are known in the art. For example, hypoxanthine, the nucleobase of the nucleoside inosine (I), can pair with adenine, cytosine, thymine, or uracil. Herein, hypoxanthine (I) is considered a complementary nucleobase to thymine (T), adenine (A), uracil (U), and cytosine (C).

[0062] As used herein, “complementary sequence(s)” or “complementary” in reference to a sequence(s) refers to two nucleobase sequences in which some, a majority, or all of the nucleobases in the two sequences are complementary nucleobases when the sequences are aligned. A “nucleobase sequence” means the order of contiguous nucleobases in a strand of linked nucleosides or a region thereof (e.g., an oligonucleotide or region thereof, or a target nucleic acid or region thereof) independent of any sugar or internucleoside linkage modification. Complementary nucleobase sequences may be nucleobase sequences of two separate strands of linked nucleosides or region thereof (e.g., an oligonucleotide and a region of a target nucleic acid, or an antisense oligonucleotide and its paired sense oligonucleotide) or complementary nucleobase sequences may be two regions of a single strand of linked nucleosides (e.g., self-complementary regions of a hairpin oligonucleotide). As used herein, when a first strand of linked nucleosides (e.g., an oligonucleotide), or region thereof, is described as being complementary to a second strand of linked nucleosides (e.g., a target nucleic acid or another oligonucleotide), it means that the nucleobase sequence of the first strand of linked nucleosides or region thereof is complementary to the nucleobase sequence of

the second strand of linked nucleosides or region thereof when aligned. Not every pair of nucleobases in the aligned nucleobase sequences needs to be a base pair match for the two sequences to be “complementary.” Rather, some mismatches are tolerated. Where complementarity is expressed as a percent, such percent represents the percent of nucleobases within one nucleobase sequence that are complementary to nucleobases within an equal length second sequence when the sequences are aligned. Unless otherwise specified, “complementary” is assumed to be at least 70%. Complementary nucleobase sequences may be 75%, 80%, 85%, 90%, 95%, or 100% complementary. For example, if a nucleobase sequence of an oligonucleotide consisting of 20 nucleosides is 80% complementary to another nucleobase sequence, then 16 of the nucleobase pairs are complementary nucleobases, and there are 4 mismatches when the sequences are aligned. If a nucleobase sequence of an oligonucleotide consisting of 20 nucleosides is at least 80% complementary to another nucleobase sequence, then 16, 17, 18, 19, or 20 of the nucleobase pairs are complementary nucleobases, and there are 0-4 mismatches when the sequences are aligned. As used herein, “fully complementary” or “100% complementary” means that each nucleobase pair of the two nucleobase sequences is complementary when the equal length sequences are aligned.

[0063] As used herein, “conjugate group” means a group of atoms that is directly or indirectly attached to an oligonucleotide. A conjugate group comprises a conjugate moiety and a conjugate linker that attaches the conjugate moiety to the oligonucleotide.

[0064] As used herein, “conjugate linker” means a single bond or a group of atoms comprising at least one bond that connects a conjugate moiety to an oligonucleotide.

[0065] As used herein, “conjugate moiety” means a group of atoms that when covalently bound to a molecule (*e.g.*, an oligonucleotide) modifies one or more properties of such molecule compared to the same molecule lacking the conjugate moiety, wherein such properties include, but are not limited to pharmacodynamics, pharmacokinetics, stability, binding, absorption, tissue distribution, cellular distribution, cellular uptake, charge, and clearance.

[0066] As used herein, “complementary region” in reference to a strand of linked nucleosides (*e.g.*, an oligonucleotide or a target nucleic acid) is a region of the strand of linked nucleosides in which the nucleobase sequence of the region is complementary with the nucleobase sequence of an equal-length region of a separate strand of linked nucleosides (*e.g.*, an oligonucleotide and a target nucleic acid, or an antisense oligonucleotide and a sense oligonucleotide), or the nucleobase sequence of an equal-length region within the strand of linked nucleosides (*e.g.*, in a “hairpin oligonucleotide”). A

complementary region of a strand of linked nucleosides may be a portion of a strand of linked nucleosides or may include the entire strand of linked nucleosides. A complementary region may include a mismatch, but the nucleobases of the terminal nucleosides of a complementary region are complementary to the nucleobases of the terminal nucleosides of the equal-length region of the separate strand of linked nucleosides or to the nucleobases of the terminal nucleosides of the equal-length region within the strand of linked nucleosides.

[0067] As used herein, “constrained ethyl” or “cEt” or “cEt sugar moiety” means a β -D ribosyl bicyclic sugar moiety wherein the second ring of the bicyclic sugar is formed via a bridge connecting the 4'-carbon and the 2'-carbon of the β -D ribosyl sugar moiety, wherein the bridge has the formula 4'-CH(CH₃)-O-2', and wherein the methyl group of the bridge is in the *S* configuration.

[0068] As used herein, “cEt nucleoside” means a nucleoside comprising a cEt sugar moiety.

[0069] As used herein, “deoxy region” means a region of 5-12 contiguous nucleosides, wherein at least 70% of the nucleosides are DNA nucleosides. Each nucleoside of a deoxy region is selected from a 2'-deoxynucleoside and 2'-substituted nucleoside. A deoxy region supports RNase H activity.

[0070] As used herein, “DNA nucleoside” means a nucleoside comprising an unmodified DNA sugar moiety. A DNA nucleoside may comprise a modified or unmodified nucleobase. A DNA nucleoside may comprise a uracil nucleobase or a modified nucleobase, or may be an abasic nucleoside.

[0071] As used herein, “DNA sugar moiety” means an unmodified DNA sugar moiety.

[0072] As used herein, “dose” means a specified quantity of active agent, e.g., a compound, oligomeric agent, for example, in a pharmaceutical composition, typically measured in metric mass units, such as milligrams (mg). A “fixed dose” refers to a quantity of active agent that is provided to each subject to whom the agent is administered, regardless of subject-specific factors, for example, weight. Typically, a fixed dose is indicated as an amount, e.g., milligrams (mg). A “weight-based dose” refers to a quantity of active agent based on weight, or body mass index of a subject to whom the active agent is administered. Typically, a weight-based dose is indicated in amount per unit of measure of body weight, such as kilograms or pounds (e.g., milligrams/kilogram, or mg/kg). As used herein, “unit dose” refers to a physically discrete composition containing a predetermined quantity of active agent (e.g., compound, oligomeric agent) intended for single administration to a subject. For example, a unit dose may be a single dose for a subject, e.g., an injection or a tablet comprising a dose for a human subject. A unit dose may contain active agent (e.g., a compound,

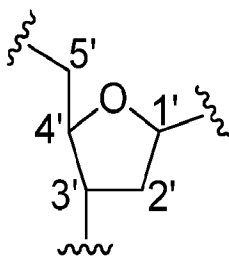
oligomeric agent) and a pharmaceutical diluent, carrier, excipient, and/or vehicle. A unit dose may be in a container, such as a vial, ampule, autoinjector device, capsule, or syringe. In certain embodiments, a unit dose is included in a single dose container, e.g., a single-dose pre-filled syringe. In certain embodiments, a unit dose is included in a multidose container, e.g., multiple single-dose pre-filled syringes supplied in a container. In certain embodiments a fixed dose and/or a weight-based dose comprises one or more unit dose(s), e.g., a fixed dose comprises administration of one or two or three unit doses.

[0073] As used herein, a “dosing regimen” refers to specific dose(s), number of dose(s), method of administration, timing of administration of doses and/or frequency of administration of doses (dosing interval) to a subject, and, if relevant, over a specific time period or treatment duration. In certain embodiments, a dosing regimen also includes additional aspects, e.g., administration in conjunction with food and/or drink, administration in conjunction with additional agent(s), administration in conjunction with other lifestyle adjustments (e.g., diet).

[0074] As used herein, “double-stranded” refers to hybridized or bound complementary regions, including those between two separate strands of linked nucleosides (e.g., an antisense oligonucleotide and a sense oligonucleotide) and those within a single strand of linked nucleosides (e.g., a hairpin oligonucleotide). Paired complementary regions of two separate strands of linked nucleosides form a “duplex” of the separate strands. Paired complementary regions of a single strand of linked nucleosides (i.e., a first region of the strand of linked nucleosides and a second region of the strand of linked nucleosides) form a “hairpin”.

[0075] As used herein, “duplex” means a structure formed by two separate strands of linked nucleosides or regions thereof (e.g., two separate oligonucleotides), at least a portion of which are complementary to and hybridize to each other. For clarity, herein a “hairpin oligonucleotide” is a single strand of linked nucleosides that comprises a region that is double-stranded and is not a duplex. A hairpin oligonucleotide that comprises at least one region that is complementary to a target nucleic acid is an antisense oligonucleotide.

[0076] As used herein, a “furanosyl sugar moiety” is a group of atoms that comprises a furanose ring and optional substituents, and is numbered according to the following structure below, with optional additional substituents at any of the 1', 2', 3', 4', and 5' positions.



[0077] As used herein, “hybridize” or “hybridization” means the act or process of two complementary regions of linked nucleosides (*e.g.*, oligonucleotides, nucleic acids) annealing together to form a double-stranded region. While not limited to a particular mechanism, the most common mechanism of hybridization involves hydrogen bonding, which may be Watson-Crick, Hoogsteen, or reversed Hoogsteen hydrogen bonding, between complementary nucleobases.

[0078] As used herein, “internucleoside linkage” means the covalent linkage between adjacent nucleosides in an oligonucleotide. As used herein, “unmodified internucleoside linkage” means a phosphodiester internucleoside linkage. As used herein, “modified internucleoside linkage” means any internucleoside linkage other than a phosphodiester internucleoside linkage. A “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. A “mesyl phosphoramidate internucleoside linkage” is a modified internucleoside linkage in which one of the non-bridging oxygen atoms of a phosphodiester internucleoside linkage is replaced with $\text{NS(=O)}_2\text{CH}_3$. Unless otherwise indicated, and in the context of linked nucleosides each comprising a furanosyl sugar moiety, an internucleoside linkage joins the 3'-carbon of one furanosyl sugar moiety to the 5'-carbon of the other furanosyl sugar moiety.

[0079] As used herein, “inverted nucleoside” means a nucleoside having a 3' to 3' and/or 5' to 5' internucleoside linkage.

[0080] As used herein, “linked nucleosides” are nucleosides that are connected in a contiguous sequence (*i.e.*, nucleosides immediately adjacent to one another, no additional nucleosides are presented between those that are linked).

[0081] As used herein, “loading dose” refers to one or more dose(s) of active agent (*e.g.*, a compound, oligomeric agent) administered to a subject during an initial phase of a dosing regimen. In certain embodiments, a loading dose is administered to achieve a desired condition in a subject, for example, a desired initial concentration of active agent, a steady state concentration of active agent, or a desired effect in the subject. In certain embodiments a single loading dose achieves the

desired state (e.g., concentration of active agent). In certain embodiments multiple loading doses achieve the desired state (e.g., concentration of active agent), wherein an “initial loading dose” means a first loading dose, and a “last loading dose” means the dose administered most recently prior to a first maintenance dose.

[0082] As used herein, “maintenance dose” refers to one or more dose(s) of active agent (e.g., a compound, oligomeric agent) administered to a subject after a loading dose. For example, a maintenance dose may be administered during a dosing phase after steady state concentration of active substance has been achieved (e.g., through administration of one or more loading dose). A maintenance dose may be administered to maintain a desired condition that results from administration of the loading dose. “Maintenance period” refers to a time period after a desired condition is achieved in a subject during which one or more maintenance doses are administered to the subject.

[0083] As used herein, a “mismatch” between two aligned strands of linked nucleosides means that the two nucleobases at a specified position of the aligned nucleobase sequences are not complementary nucleobases as defined herein.

[0084] As used herein, “modified nucleoside” means a compound or subunit comprising a sugar moiety and optionally a nucleobase, wherein the sugar moiety is modified and/or the nucleobase is modified or absent.

[0085] As used herein, “modified sugar moiety” means a group of atoms other than an unmodified sugar moiety that forms the portion of a nucleoside corresponding to a β -D-ribose sugar moiety in RNA or a β -D-deoxyribose sugar moiety in DNA. A modified sugar moiety is selected from a modified furanosyl sugar moiety, a sugar surrogate (e.g., a cyclic sugar surrogate, an acyclic sugar surrogate), or a sugar mimic.

[0086] As used herein, a “modified nucleobase” means a group of atoms other than unmodified A, T, C, U or G capable of pairing with at least one unmodified nucleobase. A “5-methylcytosine” is a modified nucleobase. Inosine (I) is a nucleoside comprising the modified nucleobase hypoxanthine.

[0087] As used herein, “motif” means a pattern of independently unmodified and/or independently modified sugar moieties, nucleobases, and/or internucleoside linkages in an oligonucleotide.

[0088] As used herein, “non-bicyclic modified sugar moiety” means a modified furanosyl sugar moiety comprising a modification, such as a substituent, that does not form a bridge between two atoms of the sugar to form a second ring.

[0089] As used herein, “nucleobase” means an unmodified nucleobase or modified nucleobase.

[0090] As used herein, “nucleobase sequence” means the order of contiguous nucleobases in a strand of linked nucleosides independent of any sugar or internucleoside linkage modification. As used herein, “the nucleobase sequence of” a reference SEQ ID NO refers only to the order of contiguous nucleobases provided in such SEQ ID NO, independent of any sugar or internucleoside linkage modification(s), and therefore, unless otherwise indicated, includes compounds wherein each sugar moiety and each internucleoside linkage, independently, is modified or unmodified, irrespective of the presence or absence of modifications indicated in the referenced SEQ ID NO.

[0091] As used herein, “nucleoside” means an “unmodified nucleoside” or a “modified nucleoside.”

[0092] As used herein, “nucleoside overhang” or “overhang” refers to unpaired nucleosides at either or both ends of an oligomeric duplex.

[0093] As used herein, “oligomeric agent” means a compound or complex comprising or consisting of at least one modified oligonucleotide and optionally one or more additional associated features selected from: (a) one or more additional modified or unmodified oligonucleotides, each of which may be hybridized to or covalently linked to the at least one modified oligonucleotide and/or to each other; (b) one or more conjugate groups, which may be covalently attached directly or indirectly to any oligonucleotide of such oligomeric agent; and (c) one or more terminal groups. Herein, where two oligonucleotides are described as being covalently attached to one another, such attachment is other than through a direct internucleoside linkage. Thus, a single, unbranched oligonucleotide comprising only direct internucleoside linkages cannot be described as two separate covalently linked oligonucleotides.

[0094] As used herein, “oligomeric compound” means a compound comprising an oligonucleotide and optionally one or more covalently linked, directly or indirectly, chemical features selected from one or more conjugate group and one or more terminal group.

[0095] As used herein, “oligonucleotide” means a strand of linked nucleosides, wherein each nucleoside and/or each internucleoside linkage of the strand of linked nucleosides may independently be modified or unmodified. Unless otherwise indicated, oligonucleotides consist of 12-80 linked nucleosides. Unless otherwise indicated, no more than 10% of the nucleosides of an oligonucleotide are abasic nucleosides. As used herein, “modified oligonucleotide” means an oligonucleotide, wherein at least one nucleoside and/or internucleoside linkage is modified. As used herein, “unmodified oligonucleotide” means an oligonucleotide consisting of unmodified

nucleosides linked by phosphodiester internucleoside linkages. An oligonucleotide may be paired with a second oligonucleotide that is complementary to the oligonucleotide to form an oligomeric duplex, or it may be unpaired.

[0096] As used herein, “pharmaceutical composition” means a mixture of substances suitable for administration to a subject. For example, a pharmaceutical composition may comprise an oligomeric agent and a sterile aqueous solution. A pharmaceutical composition may show activity in certain cell lines.

[0097] As used herein, “pharmaceutically acceptable” in reference to a substance, element, material, compound, or composition means that the substance, element, material, compound, or composition is, within the scope of sound medical judgment, suitable for use in subjects without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0098] As used herein, “pharmaceutically acceptable carrier” means an ingredient, e.g., a filler, diluent, preservative, stabilizing agent or excipient, in a pharmaceutical composition suitable for use in administering to a subject. Typically, a pharmaceutically acceptable carrier lacks pharmacological activity but is desirable in preparing a pharmaceutical composition.

[0099] 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.

[0100] As used herein, or “RAAS” refers to the renin-angiotensin-aldosterone system, a physiological/hormonal system involved in regulation of vascular tone and fluid homeostasis through regulation of blood volume, electrolyte balance and systemic vascular resistance, which, as such, is a mediator of cardiac, vascular and renal physiology. Multiple organ systems involved in RAAS include the kidneys, lungs, systemic vasculature, adrenal cortex and brain. Components of the systemic RAAS pathway that work to effectuate responses in the organ systems include angiotensinogen (AGT), renin, angiotensin I (Ang I), , angiotensin converting enzyme (ACE), angiotensin II (Ang II), and aldosterone. The first prohormone in this pathway, AGT, is manufactured by hepatocytes in the liver and secreted into circulation. Renin, secreted into circulation from the kidneys in response to decreased renal perfusion, catalyzes the conversion of AGT to Ang I, which in turn is enzymatically cleaved by ACE (expressed in vascular endothelial

cells primarily in the pulmonary circulation) to generate the biologically active Ang II. Ang II is the a primary mediator of the physiologic effects of the RAAS, and acts on vascular smooth muscle cells to contract causing vasoconstriction and increased afterload, and it stimulates production of aldosterone from the adrenal cortex. Aldosterone binds to mineralocorticoid receptors (MR) in the kidneys leading to increased sodium reabsorption, potassium excretion, and water retention which also acts to increase cardiac afterload.

[0101] As used herein, “RAAS inhibitor” refers to an agent that antagonizes or interferes with the RAAS pathway and reduces, suppresses, inhibits or blocks activity of the biologically active RAAS pathway hormones Ang II or Aldosterone, typically by targeting a component in the RAAS pathway (e.g., in the AGT-angiotensin-AT1-aldosterone axis), such as, for example, proteins, enzymes and receptors in the RAAS pathway. Examples of RAAS inhibitors include ACE inhibitors, angiotensin receptor blockers (ARBs; which block the angiotensinAT1 receptor), ARB combined with neprilysin inhibitors (ARNi), mineralocorticoid receptor blockers (MRA) and direct renin inhibitors.

[0102] As used herein, “RAAS inhibitor intolerant” or “RAAS inhibitor intolerance” refers to a diminished ability or inability of a subject to tolerate certain effects (e.g., adverse effects, side effects) that may occur with inhibition or suppression of the RAAS and/or treatment with one or more RAAS inhibitor, (e.g., an ACEi, ARB, ARNi, MRA). RAAS inhibitor intolerance can involve total intolerance to any dose of RAAS inhibitor or a partial intolerance that results in suboptimal dose (<50% of guideline-recommended target dose) that may be ineffective or less affective at inducing improvements in morbidity and mortality noted in landmark heart failure clinical trials.

[0103] As used herein, “RNA nucleoside” means a nucleoside comprising an unmodified RNA sugar moiety. An RNA nucleoside may comprise a modified or unmodified nucleobase. An RNA nucleoside may comprise a thymine nucleobase or a modified nucleobase, or may be an abasic nucleoside.

[0104] As used herein, “RNA sugar moiety” means an unmodified RNA sugar moiety.

[0105] As used herein, “RNAi agent” means an antisense agent that acts, at least in part, through RISC or Ago2 to modulate a target nucleic acid and/or a protein encoded by a target nucleic acid. RNAi agents include, but are not limited to double-stranded siRNA, single-stranded RNAi (ssRNAi), and microRNA, including microRNA mimics. RNAi agents may comprise conjugate groups and/or terminal groups. In certain embodiments, an RNAi agent modulates the amount

and/or activity of a target nucleic acid. The term RNAi agent excludes antisense agents that act through RNase H.

[0106] As used herein, “RNase H agent” means an antisense agent that acts, at least in part, through RNase H to modulate a target nucleic acid and/or protein encoded by a target nucleic acid. RNase H agents may be single-stranded or RNase H agents may be double-stranded. RNase H compounds may comprise conjugate groups and/or terminal groups. RNase H agents may modulate the amount and/or activity of a target nucleic acid. The term RNase H agent excludes antisense agents that act principally through RISC/Ago2.

[0107] As used herein, “single-stranded” in reference to a strand of linked nucleosides (e.g., an oligonucleotide) means that the strand is unpaired; that is, the strand of linked nucleosides is not part of a duplex or part of a double-stranded region. For clarity, herein a “hairpin oligonucleotide” is not a single-stranded oligonucleotide, though it may comprise a portion that is unpaired (e.g., a loop or terminal region) as well as portions that are double-stranded. Single-stranded nucleic acids (e.g., single-stranded oligonucleotides) are capable of hybridizing with complementary nucleic acids to form duplexes, at which point they are no longer single-stranded.

[0108] As used herein, “stabilized phosphate moiety” means a 5'-phosphate analog that is metabolically more stable than a 5'-phosphate as naturally occurs on DNA or RNA.

[0109] As used herein, “stereorandom” or “stereorandom chiral center” in the context of a population of molecules of identical molecular formula means a chiral center that is not intentionally controlled during synthesis, or enriched following synthesis, for a particular absolute stereochemical configuration at that chiral center. It is understood that a stereorandom chiral center may not be racemic because one absolute configuration predominates following synthesis, e.g., due to steric and electronic interactions of reagents with the reactant molecule. The stereorandom chiral center may be at the phosphorous atom of a stereorandom phosphorothioate or stereorandom mesyl phosphoramidate internucleoside linkage.

[0110] As used herein, a “strand” or “strand of linked nucleosides” means contiguous linked nucleosides connected via internucleoside linkages. A strand of linked nucleosides has a nucleobase sequence.

[0111] As used herein, “subject” means a human or non-human animal, e.g., a mammal. In certain embodiments, the subject is a human subject.

[0112] As used herein, “sugar moiety” means an unmodified sugar moiety or a modified sugar moiety.

[0113] As used herein, “symptom” of a disease means any manifestation, indication, sign, or evidence of a disease. Symptoms include subjective and objective indicia of a disease and may be perceived, experienced, detected, observed, measured, and/or quantified. A symptom may be apparent only upon invasive diagnostic testing, including, but not limited to, post-mortem tests. A symptom may be an absence of a feature, such as failing to reach expected developmental milestones.

[0114] As used herein, “target nucleic acid” means a nucleic acid, e.g., an RNA, that an antisense oligonucleotide is designed to affect. As used herein, “target RNA” means a target RNA transcript and includes pre-mRNA and/or mRNA unless otherwise specified. For example, a target RNA for an AGT target nucleic acid is an AGT RNA transcript and includes pre-mRNA and/or mRNA unless otherwise specified.

[0115] As used herein, “treating,” or “treatment,” with respect to a disease, disorder or condition, means administering a compound or agent to a subject having or at risk for developing such disease, disorder or condition. In certain embodiments, treating a disease, disorder or condition results in amelioration of at least one symptom of such disease, disorder or condition. In certain embodiments, treatment reduces, improves, and/or prevents one or more symptom(s) such that a symptom of the disease, disorder or condition is diminished, is no longer apparent, or is never apparent. In certain embodiments, treatment delays the onset of, slows the progression of, or prevents the disease, disorder or condition.

[0116] As used herein, “unmodified nucleobase” means unmodified adenine (A), unmodified thymine (T), unmodified cytosine (C), unmodified uracil (U), or unmodified guanine (G).

[0117] As used herein, an “unmodified nucleoside” means a compound or subunit comprising an unmodified sugar moiety and an unmodified nucleobase.

[0118] As used herein, “unmodified sugar moiety” means a 2'-OH(H) β -D-ribsyl sugar moiety, as found in RNA (an “unmodified RNA sugar moiety”), or a 2'-H(H) β -D-deoxyribsyl sugar moiety, as found in DNA (an “unmodified DNA sugar moiety”). Unmodified sugar moieties are furanosyl or deoxyfuranosyl sugar moieties in the β -D-ribsyl stereochemical configuration, and have one hydrogen at each of the 1', 3', and 4' positions, an oxygen at the 3' position, two hydrogens at the 5' position, and two hydrogens (DNA) or a hydrogen and an OH (RNA) at the 2' position.

[0119] II. CERTAIN EMBODIMENTS

[0120] Embodiment 1. A method for reducing AGT RNA and/or AGT protein in a subject intolerant, or at risk of being intolerant, to treatment with a renin-angiotensin-aldosterone system (RAAS) inhibitor, comprising administering an oligomeric compound or salt thereof to a subject having or at risk for heart failure; wherein the subject is intolerant, or is at risk of being intolerant, to treatment with a RAAS inhibitor; and wherein the amount of AGT protein in the subject is reduced by at least 70%, at least 75%, at least 80% or at least 85% but less than 95% in the subject; wherein the oligomeric compound is a GalNAc-conjugated modified oligonucleotide, wherein the modified oligonucleotide is represented by the following chemical notation (5' to 3'):

${}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 4) or a salt thereof; wherein:

A = an adenine nucleobase,

${}^m\text{C}$ = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

k = a cEt sugar moiety,

d = an unmodified DNA sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage;

and wherein GalNAc is an N-acetyl galactosamine conjugate moiety.

[0121] Embodiment 2. A method of treating heart failure in a subject, comprising administering an oligomeric compound or a salt thereof to a subject having or at risk of having heart failure, wherein the subject is or is at risk of being intolerant to treatment with a RAAS inhibitor; wherein treatment results in amelioration of one or more symptoms and/or lack of progression of heart failure; wherein the oligomeric compound is a GalNAc-conjugated modified oligonucleotide, wherein the modified oligonucleotide is represented by the following chemical notation (5' to 3'):

${}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 4) or a salt thereof; wherein:

A = an adenine nucleobase,

${}^m\text{C}$ = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,
 k = a cEt sugar moiety,
 d = an unmodified DNA sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage;

and wherein GalNAc is an N-acetyl galactosamine conjugate moiety.

[0122] Embodiment 3. A method of treating heart failure in a subject, comprising administering about 50 mg to about 200 mg an oligomeric compound or a salt thereof to a subject; wherein administering oligomeric compound results in amelioration of one or more symptoms and/or lack of progression of heart failure;

wherein the oligomeric compound is a GalNAc-conjugated modified oligonucleotide, wherein the modified oligonucleotide is represented by the following chemical notation (5' to 3'):

${}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 4) or a salt thereof; wherein:

A = an adenine nucleobase,
 ${}^m\text{C}$ = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 k = a cEt sugar moiety,
 d = an unmodified DNA sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage;

and wherein GalNAc is an N-acetyl galactosamine conjugate moiety.

[0123] Embodiment 4. Use of an oligomeric compound or a salt thereof for treating heart failure in a subject intolerant to, or at risk of being intolerant to, treatment with a RAAS inhibitor, wherein:

heart failure in the subject does not progress or one or more symptoms are ameliorated;

wherein the oligomeric compound is a GalNAc-conjugated modified oligonucleotide, wherein the modified oligonucleotide is represented by the following chemical notation (5' to 3'):

${}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 4) or a salt thereof; wherein:

A = an adenine nucleobase,
 ${}^m\text{C}$ = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 k = a cEt sugar moiety,
 d = an unmodified DNA sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage;

and wherein GalNAc is an N-acetyl galactosamine conjugate moiety.

[0124] Embodiment 5. Use of 50 mg to 200 mg of an oligomeric compound or a salt thereof for treating heart failure in a subject having or at risk for heart failure; wherein the oligomeric compound is a GalNAc-conjugated modified oligonucleotide, wherein the modified oligonucleotide is represented by the following chemical notation (5' to 3'):

${}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 4) or a salt thereof; wherein:

A = an adenine nucleobase,
 ${}^m\text{C}$ = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 k = a cEt sugar moiety,
 d = an unmodified DNA sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage;

and wherein GalNAc is an N-acetyl galactosamine conjugate moiety.

[0125] Embodiment 6. Use of an oligomeric compound or a salt thereof for reducing AGT RNA and/or AGT protein in a subject intolerant, or at risk of being intolerant, to treatment with a renin-angiotensin-aldosterone system (RAAS) inhibitor; wherein the oligomeric compound is a GalNAc conjugated modified oligonucleotide, wherein the modified oligonucleotide is represented by the following chemical notation (5' to 3'):

${}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 4) or a salt thereof; wherein:

A = an adenine nucleobase,
 ${}^m\text{C}$ = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 k = a cEt sugar moiety,
 d = an unmodified DNA sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage;

wherein GalNAc= is an N-acetyl galactosamine conjugate moiety;

and wherein the oligomeric compound reduces AGT protein in a subject by at least 70%, at least 75%, at least 80% or at least 85% but less than 95%.

[0126] Embodiment 7. A method for administering an oligomeric compound to a subject, comprising administering 60 mg to 120 mg of an oligomeric compound or salt thereof to a subject having or at risk for heart failure with reduced ejection fraction (HFrEF); wherein the oligomeric compound is a GalNAc-conjugated modified oligonucleotide, wherein the modified oligonucleotide is represented by the following chemical notation (5' to 3'):

^mC_{es}G_{eo}^mC_{ko}T_{ds}G_{ds}A_{ds}T_{ds}T_{ds}G_{ds}T_{ds}^mC_{ds}^mC_{ds}G_{ko}G_{ks}G_e (SEQ ID NO: 4) or a salt thereof; 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,
 k = a cEt sugar moiety,
 d = an unmodified DNA sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage;

and wherein GalNAc is an N-acetyl galactosamine conjugate moiety.

[0127] Embodiment 8. A method for reducing AGT RNA and/or AGT protein in a subject, comprising administering 60 mg to 120 mg of an oligomeric compound or salt thereof to a subject having or at risk for heart failure with reduced ejection fraction (HFrEF); wherein the oligomeric compound is a GalNAc-conjugated modified oligonucleotide, wherein the modified oligonucleotide is represented by the following chemical notation (5' to 3'):

${}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 4) or a salt thereof; wherein:

A = an adenine nucleobase,

${}^m\text{C}$ = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

k = a cEt sugar moiety,

d = an unmodified DNA sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage;

and wherein GalNAc is an N-acetyl galactosamine conjugate moiety.

[0128] Embodiment 9. Use of 60 mg to 120 mg of an oligomeric compound or a salt thereof for treating a subject having or at risk for heart failure with reduced ejection fraction (HFrEF); wherein the oligomeric compound is a GalNAc conjugated modified oligonucleotide, wherein the modified oligonucleotide is represented by the following chemical notation (5' to 3'):

${}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 4) or a salt thereof; wherein:

A = an adenine nucleobase,

${}^m\text{C}$ = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

k = a cEt sugar moiety,

d = an unmodified DNA sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage;

wherein GalNAc= is an N-acetyl galactosamine conjugate moiety

[0129] Embodiment 10. Use of 60 mg to 120 mg of an oligomeric compound or a salt thereof for reducing AGT RNA and/or AGT protein in a subject having or at risk for heart failure with reduced ejection fraction (HFrEF);

wherein the oligomeric compound is a GalNAc conjugated modified oligonucleotide, wherein the modified oligonucleotide is represented by the following chemical notation (5' to 3'):

${}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 4) or a salt thereof; wherein:

A = an adenine nucleobase,

${}^m\text{C}$ = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

k = a cEt sugar moiety,

d = an unmodified DNA sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage;

wherein GalNAc= is an N-acetyl galactosamine conjugate moiety.

[0130] Embodiment 11. The method or use of any one of embodiments 1-10, wherein the oligomeric compound is represented by the following chemical notation (5' to 3'):

THA-C6-GalNAc₃- ${}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 5) or a salt thereof; wherein,

A = an adenine nucleobase,

${}^m\text{C}$ = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

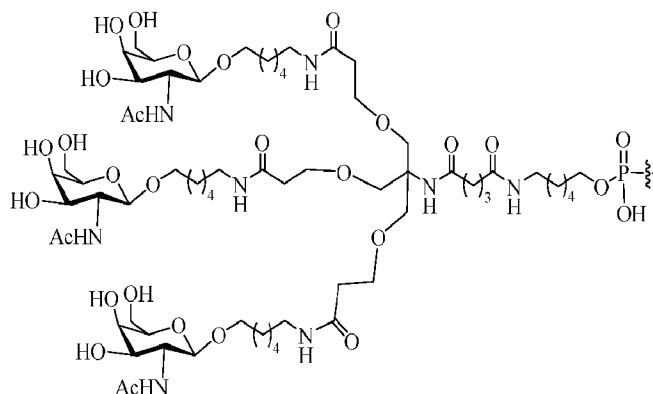
k = a cEt sugar moiety,

d = an unmodified DNA sugar moiety,

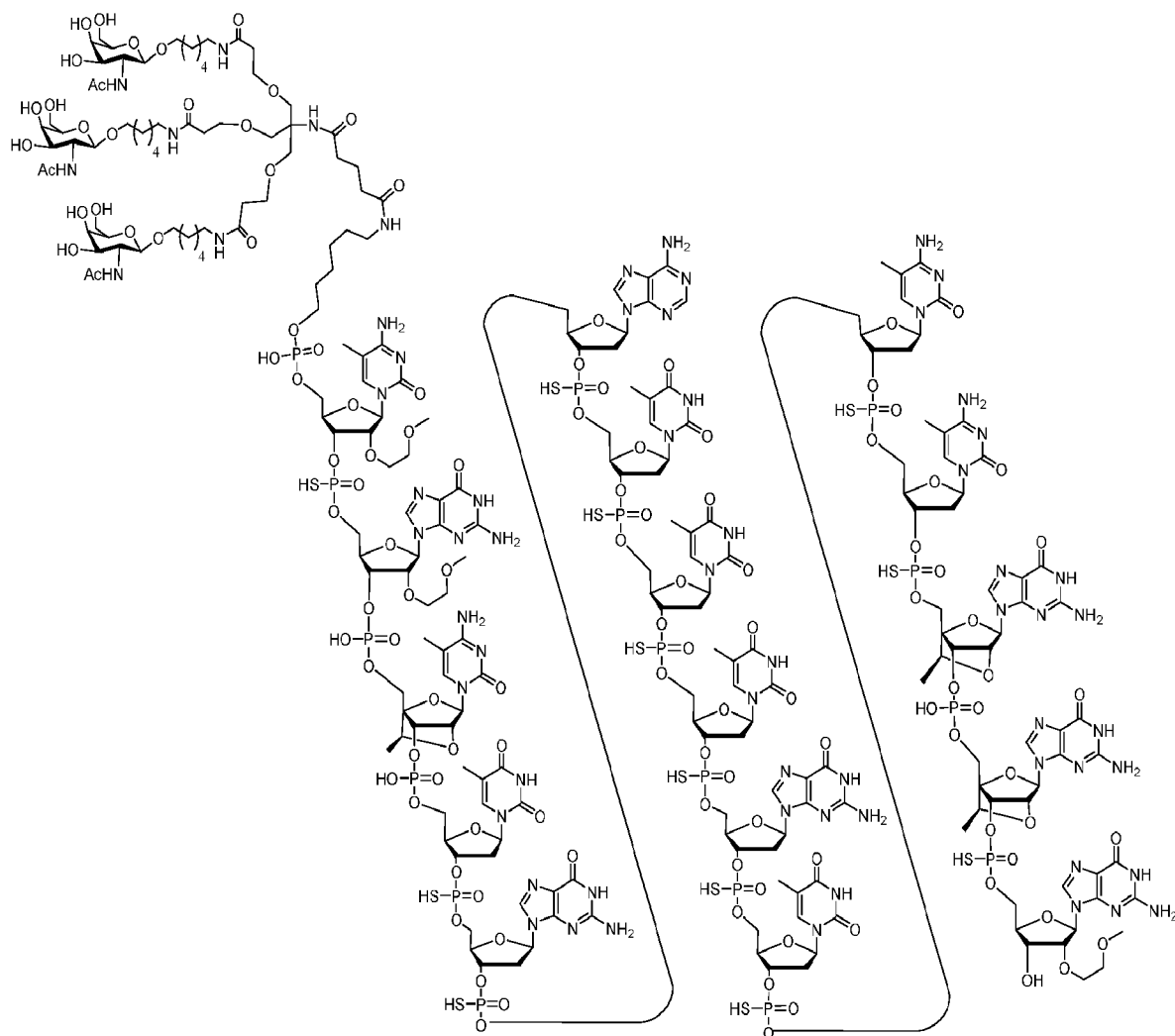
s = a phosphorothioate internucleoside linkage,

o = a phosphodiester internucleoside linkage, and

THA-C6-GalNAc₃=



[0131] Embodiment 12. The method or use of any one of embodiments 1-10, wherein the oligomeric compound is represented by the following Structure 1:

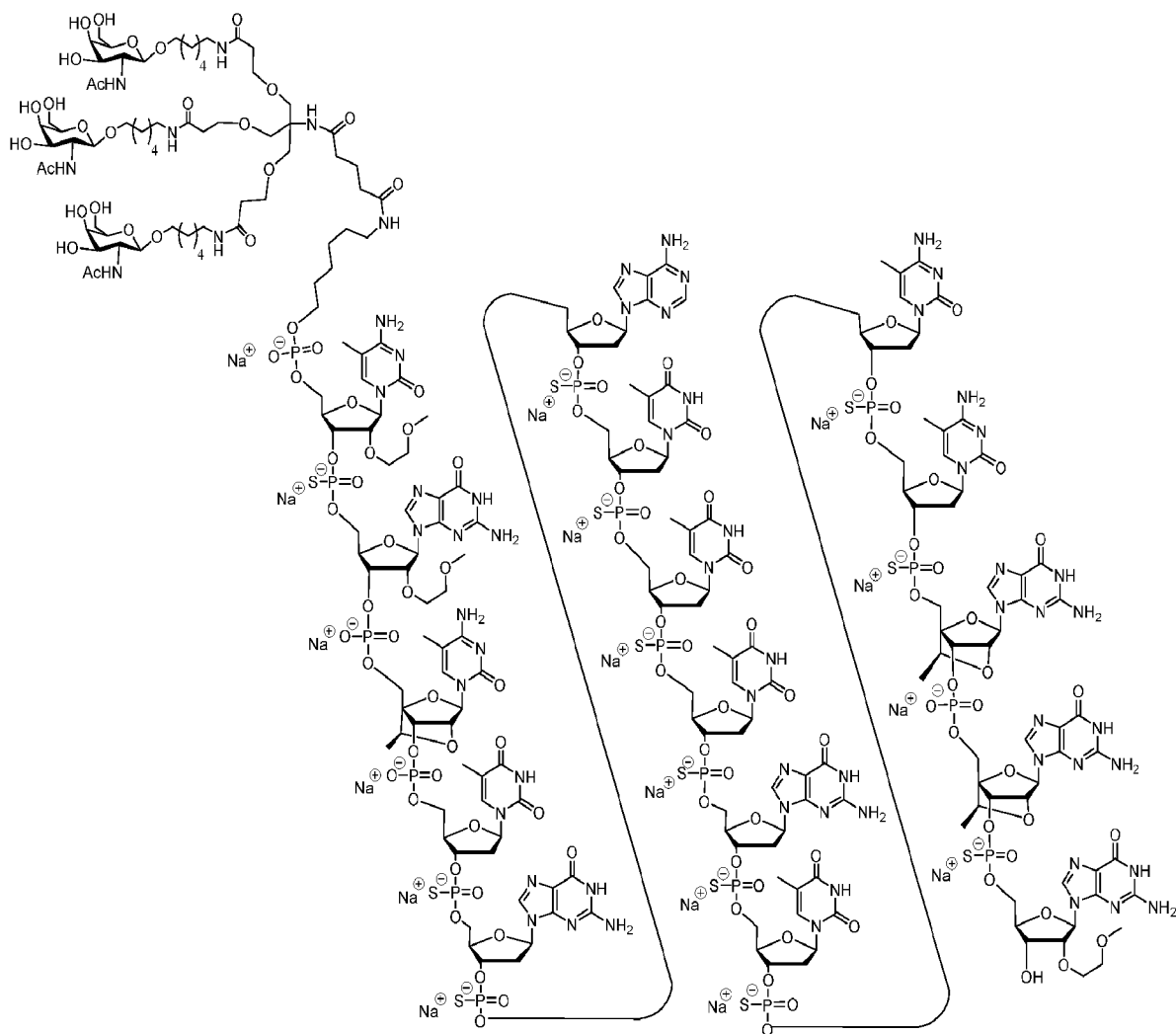


(SEQ ID NO: 5),

or a salt thereof.

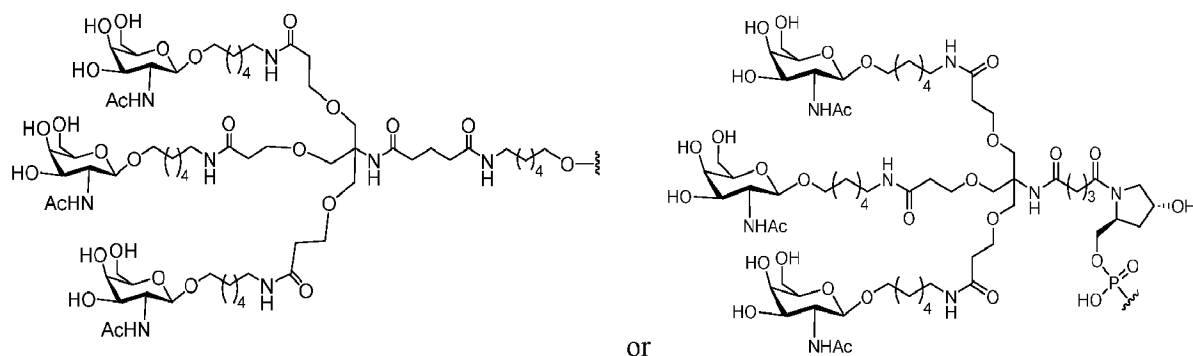
[0132] Embodiment 13. The method or use of any one of embodiments 1-12, wherein the oligomeric compound is a sodium salt or a potassium salt.

[0133] Embodiment 14. The method or use of any one of embodiments 1-10, wherein the oligomeric compound is a sodium salt represented by the following Structure 2:



(SEQ ID NO: 5).

[0134] Embodiment 15. The method or use of any one of embodiments 1-10, wherein the conjugate group comprises the following structure:



[0135] Embodiment 16. The method or use of any one of embodiments 1-10, wherein the conjugate group is attached to the 5'-terminal nucleoside of the modified oligonucleotide or the 3'-terminal nucleoside of the modified oligonucleotide.

[0136] Embodiment 17. The method or use of any one of embodiments 1-16, wherein the amount of AGT protein in the liver of the subject is reduced.

[0137] Embodiment 18. The method or use of any one of embodiments 1-17, wherein the amount of AGT protein in the blood, serum or plasma of the subject is reduced.

[0138] Embodiment 19. The method or use of any one of embodiments 1-6 and 11-18, wherein the subject has or is at risk for, or the heart failure is, heart failure with reduced ejection fraction (HFrEF), heart failure with mid-range ejection fraction (HFmrEF), heart failure with improved ejection fraction (HFimpEF), or heart failure with preserved ejection fraction (HFpEF).

[0139] Embodiment 20. The method or use of any one of embodiments 1-19, wherein the subject has a left ventricular ejection fraction of about 50% or less, about 40% or less, or about 35% or less, or about 30% or less.

[0140] Embodiment 21. The method or use of any one of embodiments 1-20, wherein the subject has one or more of asymptomatic left ventricular dysfunction (ALVD), asymptomatic or symptomatic valvular heart disease, left ventricular hypertrophy, left ventricular fibrosis, left ventricular dilatation, and left ventricular hypocontractility.

[0141] Embodiment 22. The method or use of any one of embodiments 1-21, wherein a decrease in the amount of AGT RNA and/or AGT protein in the subject is less than 95%, or less than 94%, or less than 93%, or less than 92%, or less than 91%, or less than 90% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric compound or salt thereof.

[0142] Embodiment 23. The method or use of any one of embodiments 1-21, wherein the amount of AGT RNA and/or AGT protein in the subject is decreased by no more than 85%, or no more than 86%, or no more than 87%, or no more than 88%, or no more than 89%, or no more than 90%, or no more than 91%, or no more than 92%, or no more than 93%, or no more than 94%, or no more than 95% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric compound or salt thereof.

[0143] Embodiment 24. The method or use of any one of embodiments 1-21, wherein the amount of AGT RNA and/or AGT protein is decreased by at least 70%, at least 75%, at least 80% or at least

85% and less than 95% compared to the amount of AGT protein prior to administering the oligomeric compound or salt thereof.

[0144] Embodiment 25. The method or use of any one of embodiments 1-21, wherein the amount of AGT RNA and/or AGT protein is decreased by at least 70%, at least 75%, at least 80% or at least 85% and less than 90% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric compound or salt thereof.

[0145] Embodiment 26. The method or use of any one of embodiments 1-21, wherein the amount of AGT RNA and/or AGT protein in the subject is decreased by at least 75% and less than 95%, less than 94%, less than 93%, less than 92%, less than 91%, less than 90%, less than 89%, less than 88%, or less than 85% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric compound or salt thereof.

[0146] Embodiment 27. The method or use of any one of embodiments 1-26, wherein the oligomeric compound or salt thereof is the only RAAS inhibitor administered to the subject.

[0147] Embodiment 28. The method or use of any one of embodiments 1-26, wherein the subject has been previously treated with a GDMT for heart failure.

[0148] Embodiment 29. The method or use of any one of embodiments 1-26, wherein the subject has been previously treated with a RAAS inhibitor.

[0149] Embodiment 30. The method or use of any one of embodiments 1-26, wherein the subject has been previously treated with an ACE inhibitor, an ARB, an ARNi, a MRA and/or a direct renin inhibitor.

[0150] Embodiment 31. The method or use of any one of embodiments 1-26, wherein the subject is being treated concurrently with a RAAS inhibitor in addition to the oligomeric compound.

[0151] Embodiment 32. The method or use of any one of embodiments 1-26, wherein the subject is being treated concurrently with an ACE inhibitor, ARB an ARNi, a MRA and/or a renin inhibitor.

[0152] Embodiment 33. The method of any one of embodiments 1-26, comprising administering the oligomeric compound or salt thereof and simultaneously or sequentially administering: (i) a RAAS inhibitor or (ii) an ACE inhibitor, ARB, ARNi, MRA or direct renin inhibitor to the subject.

[0153] Embodiment 34. The method of embodiment 33, wherein the oligomeric compound or salt thereof and (i) or (ii) are administered simultaneously in a single composition.

[0154] Embodiment 35. The method or use of any one of embodiments 31-34, wherein the RAAS inhibitor, ACE inhibitor, ARB, ARNi, MRA or a direct renin inhibitor is administered at less than the Guideline-recommended target dose for treatment of HFrEF.

[0155] Embodiment 36. The method or use of embodiment 35, wherein the RAAS inhibitor, ACE inhibitor, ARB, ARNi, MRA or renin inhibitor is administered at less than about 70%, less than about 60%, less than about 50%, or less than about 40% of the Guideline-recommended target dose for treatment of HFrEF.

[0156] Embodiment 37. The method or use of any one of embodiments 28-36, wherein the RAAS inhibitor, ACE inhibitor, ARB, ARNi, MRA or renin inhibitor is administered at a frequency that is less than the Guideline-recommended dosing regimen for treatment of HFrEF.

[0157] Embodiment 38. The method or use of any one of embodiments 1-27, wherein the subject is treated concurrently with a neprilysin inhibitor.

[0158] Embodiment 39. The method or use of any one of embodiments 1-27, further comprising simultaneously or sequentially administering a neprilysin inhibitor to the subject.

[0159] Embodiment 40. The method or use of embodiment 38 or embodiment 39, wherein the neprilysin inhibitor is sacubitril.

[0160] Embodiment 41. The method or use of embodiment 39 or embodiment 40, further comprising simultaneously or sequentially administering an ARB to the subject.

[0161] Embodiment 42. The method or use of embodiment 41, wherein the ARB is valsartan.

[0162] Embodiment 43. The method or use of any one of embodiments 1-42, wherein the subject has asymptomatic left ventricular dysfunction (ALVD).

[0163] Embodiment 44. The method or use of any one of embodiments 1-42, wherein the subject has structural and/or functional abnormalities of the pericardium, myocardium and/or a cardiac valve.

[0164] Embodiment 45. The method or use of any one of embodiments 1-42, wherein the subject has one or more of asymptomatic or symptomatic valvular heart disease, left ventricular hypertrophy, left ventricular fibrosis, left ventricular dilatation, and left ventricular hypocontractility.

[0165] Embodiment 46. The method or use of any one of embodiments 1-45, wherein the subject has or is at risk of having angioedema or asthma.

[0166] Embodiment 47. The method or use of any one of embodiments 1-46, wherein the subject has renal insufficiency.

[0167] Embodiment 48. The method or use of embodiment 47, wherein the subject has an estimated glomerular filtration rate (eGFR) of between 30 and 90 ml/min/1.73 m², between 30 and 89 ml/min/1.73 m², between 30 and 80 ml/min/1.73 m², between 20 and 89 ml/min/1.73 m², between 20 and 80 ml/min/1.73 m², between 45 and 89 ml/min/1.73 m², between 40 and 89 ml/min/1.73 m², between 40 and 80 ml/min/1.73 m², between 60 and 89 ml/min/1.73 m², between 30 and 60 ml/min/1.73 m², between 30 and 59 ml/min/1.73 m², between 40 and 60 ml/min/1.73 m², between 30 and 44 ml/min/1.73 m², between 35 and 45 ml/min/1.73 m², between 15 and 44 ml/min/1.73 m², between 15 and 29 ml/min/1.73 m², less than about 90 ml/min/1.73 m², less than about 89 ml/min/1.73 m², less than about 80 ml/min/1.73 m², less than about 70 ml/min/1.73 m², less than about 60 ml/min/1.73 m², less than about 59 ml/min/1.73 m², less than about 45 ml/min/1.73 m², less than about 44 ml/min/1.73 m², less than about 40 ml/min/1.73 m², less than about 30 ml/min/1.73 m², less than about 29 ml/min/1.73 m², or less than about 15 ml/min/1.73 m².

[0168] Embodiment 49: The method or use of any one of embodiments 1-48, wherein administering or use of the oligomeric compound or salt thereof comprises administering or use of a fixed dose of the oligomeric compound or salt thereof within the range of about 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 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 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 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 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 150 mg, 100 mg to 140 mg, 100 mg to 120 mg, 100 mg to 110 mg, 110 mg to 150 mg, 110 mg to 140 mg, 110 mg to 130 mg, 110 mg to 120 mg, 120 mg to 150 mg, 120 mg to 140 mg, 120 mg to 130 mg, 130 mg to 150 mg, 130 mg to 140 mg, 140 mg to 150 mg, 55 mg to 125 mg, 55 mg to 115 mg, 55 mg to 105 mg, 55 mg to 95 mg, 55 mg to 85 mg, 55 mg to 75 mg, 55 mg to 65 mg, 65 mg to 125 mg, 65 mg to 115 mg, 65 mg to 105 mg, or 65 mg to 95 mg, 65 mg to 85 mg, 65 mg to 75 mg, 75 mg to 125 mg, 75 mg to 115 mg, 75 mg to 105 mg, 75 mg to 95 mg, 75 mg to 85 mg, 85 mg to 125 mg, 85 mg to 115 mg, 85 mg to 105 mg, or 85 mg to 95 mg.

[0169] Embodiment 50: The method or use of any one of embodiments 1-48, wherein administering or use of the oligomeric compound or salt thereof comprises administering or use of a fixed dose of the oligomeric compound or salt thereof within the range of about 50 mg to about 150 mg, about 50 mg to about 140 mg, about 50 mg to about 120 mg, about 50 mg to about 110 mg, about 50 mg to about 100 mg, about 50 mg to about 80 mg, about 50 mg to about 70 mg, about 50 mg to about 60 mg, about 60 mg to about 150 mg, about 60 mg to about 140 mg, about 60 mg to about 120 mg, about 60 mg to about 110 mg, about 60 mg to about 100 mg, about 60 mg to about 80 mg, about 60 mg to about 70 mg, about 70 mg to about 150 mg, about 70 mg to about 140 mg, about 70 mg to about 120 mg, about 70 mg to about 110 mg, about 70 mg to about 100 mg, about 70 mg to about 80 mg, about 80 mg to about 150 mg, about 80 mg to about 140 mg, about 80 mg to about 120 mg, about 80 mg to about 110 mg, about 80 mg to about 100 mg, about 80 mg to about 90 mg, about 90 mg to about 150 mg, about 90 mg to about 140 mg, about 90 mg to about 120 mg, about 90 mg to about 110 mg, about 90 mg to about 100 mg, about 100 mg to about 150 mg, about 100 mg to about 140 mg, about 100 mg to about 120 mg, about 100 mg to about 110 mg, about 110 mg to about 150 mg, about 110 mg to about 140 mg, about 110 mg to about 130 mg, about 110 mg to about 120 mg, about 120 mg to about 150 mg, about 120 mg to about 140 mg, about 120 mg to about 130 mg, about 130 mg to about 150 mg, about 130 mg to about 140 mg, about 140 mg to about 150 mg, about 55 mg to about 125 mg, about 55 mg to about 115 mg, about 55 mg to about 105 mg, about 55 mg to about 95 mg, about 55 mg to about 85 mg, about 55 mg to about 75 mg, about 55 mg to about 65 mg, about 65 mg to about 125 mg, about 65 mg to about 115 mg, about 65 mg to about 105 mg, or about 65 mg to about 95 mg, about 65 mg to about 85 mg, about 65 mg to about 75 mg, about 75 mg to about 125 mg, about 75 mg to about 115 mg, about 75 mg to about 105 mg, about 75 mg to about 95 mg, about 75 mg to about 85 mg, about 85 mg to about 125 mg, about 85 mg to about 115 mg, about 85 mg to about 105 mg, or about 85 mg to about 95 mg.

[0170] Embodiment 51. The method or use of any one of embodiments 1-48, wherein administering or use of the oligomeric compound or salt thereof comprises administering or use of a fixed dose of at least about 50 mg and less than about 150 mg, at least about 50 mg and less than about 145 mg, at least about 50 mg and less than about 140 mg, at least about 50 mg and less than about 135 mg, at least about 50 mg and less than about 130 mg, at least about 50 mg and less than about 125 mg, at least about 50 mg and less than about 120 mg, at least about 50 mg and less than about 115 mg, at least about 50 mg and less than about 110 mg, at least about 50 mg and less than about 105 mg, at

least about 50 mg and less than about 100 mg, at least about 50 mg and less than about 95 mg, at least about 50 mg and less than about 90 mg, at least about 50 mg and less than about 85 mg, at least about 50 mg and less than about 80 mg, at least about 50 mg and less than about 75 mg, at least about 50 mg and less than about 70 mg, at least about 50 mg and less than about 65 mg, at least about 55 mg and less than about 65 mg, at least about 60 mg and less than about 150 mg, at least about 60 mg and less than about 145 mg, at least about 60 mg and less than about 140 mg, at least about 60 mg and less than about 135 mg, at least about 60 mg and less than about 130 mg, at least about 60 mg and less than about 125 mg, at least about 60 mg and less than about 120 mg, at least about 60 mg and less than about 115 mg, at least about 60 mg and less than about 110 mg, at least about 60 mg and less than about 105 mg, at least about 60 mg and less than about 100 mg, at least about 60 mg and less than about 95 mg, at least about 70 mg and less than about 150 mg, at least about 70 mg and less than about 145 mg, at least about 70 mg and less than about 140 mg, at least about 70 mg and less than about 135 mg, at least about 70 mg and less than about 130 mg, at least about 70 mg and less than about 125 mg, at least about 70 mg and less than about 120 mg, at least about 70 mg and less than about 115 mg, at least about 70 mg and less than about 110 mg, at least about 70 mg and less than about 105 mg, at least about 70 mg and less than about 100 mg, at least about 70 mg and less than about 95 mg, at least about 80 mg and less than about 150 mg, at least about 80 mg and less than about 145 mg, at least about 80 mg and less than about 140 mg, at least about 80 mg and less than about 135 mg, at least about 80 mg and less than about 130 mg, at least about 80 mg and less than about 125 mg, at least about 80 mg and less than about 120 mg, at least about 80 mg and less than about 115 mg, at least about 80 mg and less than about 110 mg, at least about 80 mg and less than about 105 mg, at least about 80 mg and less than about 100 mg, at least about 80 mg and less than about 95 mg, or at least about 85 mg and less than about 95 mg of the oligomeric compound or salt thereof.

[0171] Embodiment 52. The method or use of any one of embodiments 1-48, wherein administering or use of the oligomeric compound or salt thereof comprises administering or use of a fixed dose of 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, or about 150 mg of the oligomeric compound or salt thereof.

[0172] Embodiment 53. The method or use of any one of embodiments 1-48, wherein administering or use of the oligomeric compound or salt thereof comprises administering or use of a fixed dose of 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, or 150 mg of the oligomeric compound or salt thereof.

[0173] Embodiment 54. The method or use of any one of embodiments 1-48, wherein administering or use comprises administering or use of a fixed dose of about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, or about 100 mg of the oligomeric compound or salt thereof.

[0174] Embodiment 55. The method or use of any one of embodiments 1-48, wherein the administering or use comprises administering or use of a fixed dose of 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, or 100 mg of the oligomeric compound or salt thereof.

[0175] Embodiment 56. The method or use of any one of embodiments 1-48, wherein the administering or use comprises administering or use of a fixed dose of the oligomeric compound or salt thereof within the range of about 55 mg to about 100 mg, about 60 mg to about 100 mg, about 65 mg to about 100 mg, about 70 mg to about 100 mg, about 75 mg to about 100 mg, about 80 mg to about 100 mg, about 85 mg to about 100 mg, about 85 mg to about 100 mg, or about 85 mg to about 95 mg.

[0176] Embodiment 57. The method or use of any one of embodiments 1-48, comprising administering or use of a fixed dose of about 55 mg of the oligomeric compound or salt thereof.

[0177] Embodiment 58. The method or use of any one of embodiments 1-48, comprising administering or use of a fixed dose of about 60 mg of the oligomeric compound or salt thereof.

[0178] Embodiment 59. The method or use of any one of embodiments 1-48, comprising administering or use of a fixed dose of about 65 mg of the oligomeric compound or salt thereof.

[0179] Embodiment 60. The method or use of any one of embodiments 1-48, comprising administering or use of a fixed dose of about 70 mg of the oligomeric compound or salt thereof.

[0180] Embodiment 61. The method or use of any one of embodiments 1-48, comprising administering or use of a fixed dose of about 75 mg of the oligomeric compound or salt thereof.

[0181] Embodiment 62. The method or use of any one of embodiments 1-48, comprising administering or use of a fixed dose of about 80 mg of the oligomeric compound or salt thereof.

[0182] Embodiment 63. The method or use of any one of embodiments 1-48, comprising administering or use of a fixed dose of about 85 mg of the oligomeric compound or salt thereof.

[0183] Embodiment 64. The method or use of any one of embodiments 1-48, comprising administering or use of a fixed dose of about 90 mg of the oligomeric compound or salt thereof.

[0184] Embodiment 65. The method or use of any one of embodiments 1-48, comprising administering or use of a fixed dose of about 95 mg of the oligomeric compound or salt thereof.

[0185] Embodiment 66. The method or use of any one of embodiments 1-48, comprising administering or use of a fixed dose of about 100 mg of the oligomeric compound or salt thereof.

[0186] Embodiment 67. The method or use of any one of embodiments 1-48, comprising administering or use of a fixed dose of 55 mg to 105 mg of the oligomeric compound or salt thereof.

[0187] Embodiment 68. The method or use of any one of embodiments 1-48, comprising administering or use of a unit dose of 60 mg of the oligomeric compound or salt thereof.

[0188] Embodiment 69. The method or use of any one of embodiments 1-48, comprising administering or use of a fixed dose of 65 mg of the oligomeric compound or salt thereof.

[0189] Embodiment 70. The method or use of any one of embodiments 1-48, comprising administering or use of a fixed dose of 70 mg of the oligomeric compound or salt thereof.

[0190] Embodiment 71. The method or use of any one of embodiments 1-48, comprising administering or use of a fixed dose of 75 mg of the oligomeric compound or salt thereof.

[0191] Embodiment 72. The method or use of any one of embodiments 1-48, comprising administering or use of a fixed dose of 80 mg of the oligomeric compound or salt thereof.

[0192] Embodiment 73. The method or use of any one of embodiments 1-48, comprising administering or use of a fixed dose of 85 mg of the oligomeric compound or salt thereof.

[0193] Embodiment 74. The method or use of any one of embodiments 1-48, comprising administering or use of a fixed dose of 90 mg of the oligomeric compound or salt thereof.

[0194] Embodiment 75. The method or use of any one of embodiments 1-48, comprising administering or use of a fixed dose of 95 mg of the oligomeric compound or salt thereof.

[0195] Embodiment 76. The method or use of any one of embodiments 1-48, comprising administering or use of a fixed dose of 100 mg of the oligomeric compound or salt thereof.

[0196] Embodiment 77. The method or use of any one of embodiments 1-48, wherein the oligomeric compound or salt thereof is ION904 or a salt thereof.

[0197] Embodiment 78. The method of any one of embodiments 1-77, wherein the oligomeric compound or salt thereof is administered once about every 4 weeks or once about every 28 days.

[0198] Embodiment 79. The method of any one of embodiments 1-77, wherein the oligomeric compound or salt thereof is administered at an interval of about once a month, about once every two months, or about once every three months.

[0199] Embodiment 80. The method of any one of embodiments 1-77, wherein the oligomeric compound or salt thereof is administered about once every 2 weeks, about once every 3 weeks, about once every 4 weeks, about once every 5 weeks, about once every 6 weeks, about once every 7 weeks, about once every 8 weeks, about once every 9 weeks, or about once every 10 weeks.

[0200] Embodiment 81. The method of any one of embodiments 1-77, wherein the oligomeric compound or salt thereof is administered once every 4 weeks or once every 28 days.

[0201] Embodiment 82. The method of any one of embodiments 1-77, wherein the oligomeric compound or salt thereof is administered at an interval of once a month, once every two months, or once every three months.

[0202] Embodiment 83. The method of any one of embodiments 1-77, wherein the oligomeric compound or salt thereof is administered once every 2 weeks, once every 3 weeks, once every 4 weeks, once every 5 weeks, once every 6 weeks, once every 7 weeks, once every 8 weeks, once every 9 weeks, or once every 10 weeks.

[0203] Embodiment 84. The method or use of any one of embodiments 1-83, wherein administering or use comprises administering or use of a fixed dose of 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, or 100 mg of the oligomeric compound or salt thereof once every 3 weeks, once every 4 weeks, once every 5 weeks or once every 6 weeks.

[0204] Embodiment 85. The method or use of any one of embodiments 1-83, wherein administering or use comprises administering or use of a fixed dose of about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, or about 100 mg of the oligomeric compound or salt thereof once about every 3 weeks, once about every 4 weeks, once about every 5 weeks or once about every 6 weeks, wherein the oligomeric compound is formulated for parenteral administration.

[0205] Embodiment 86. The method or use of embodiment 85, wherein administering or use comprises administering or use of a fixed dose of about 60 mg, about 70 mg, about 80 mg, about 90 mg, or about 100 mg of the oligomeric compound or salt thereof once about every 25 days, once

about every 26 days, once about every 27 days, once about every 28 days, once about every 29 days, once about every 30 days, or once about every 31 days, wherein the oligomeric compound is formulated for parenteral administration.

[0206] Embodiment 87. The method or use of embodiment 85, wherein administering or use comprises administering or use of a fixed dose of 60 mg or about 60 mg, or 90 mg or about 90 mg of the oligomeric compound or salt thereof once every 28 days or about every 28 days, or once every 4 weeks or about every 4 weeks, or once a month or about once a month, wherein the oligomeric compound is formulated for subcutaneous administration.

[0207] Embodiment 88. The method or use of embodiment 85, wherein administering or use comprises administering or use of a fixed dose of about 60 mg or about 90 mg of the oligomeric compound or salt thereof once about every 28 days or once about every 4 weeks, or once about every month, wherein the oligomeric compound is formulated for subcutaneous administration.

[0208] Embodiment 89. The method or use of any one of embodiments 1-88, wherein the oligomeric compound or salt thereof comprises administering or use of a loading dose.

[0209] Embodiment 90. The method or use of embodiment 89, wherein the administering or use comprises one or more maintenance doses of the oligomeric compound or salt thereof.

[0210] Embodiment 91. The method or use of embodiment 90, wherein the loading dose comprises a greater amount of the oligomeric compound or salt thereof than a maintenance dose.

[0211] Embodiment 92. The method or use of embodiment 90, wherein the loading dose and the maintenance dose comprises the same amount of the oligomeric compound or salt thereof.

[0212] Embodiment 93. The method or use of any one of embodiments 1-92, wherein the administration or use of the oligomeric compound or salt thereof is effective to decrease the amount of AGT RNA and/or AGT protein in the subject by at least 70%, at least 75%, at least 80%, or at least 85% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration or use of the oligomeric compound or salt thereof.

[0213] Embodiment 94. The method or use of any one of embodiments 1-93, wherein such method or use is effective to treat heart failure and/or ameliorate one or more symptoms of heart failure, but does not significantly reduce systolic blood pressure and/or diastolic blood pressure in a subject having, or at risk for, heart failure.

[0214] Embodiment 95. The method or use of any one of embodiments 1-93, wherein such method or use improves cardiac function, reduces cardiac dilation, reduces cardiac fibrosis, reverses or

attenuates cardiac remodeling, increases LVEF, improves left ventricular end systolic volume (LVESV) or left ventricular indexed end systolic volume (LVESVi), improves left ventricular end diastolic volume (LVEDV), improves left ventricle (LV) strain, improves 6-minute walk test, and/or improves quality of life in the subject having, or at risk for, heart failure.

[0215] Embodiment 96. The method or use of any one of embodiments 1-93, wherein such method or use decreases the level of NT-proBNP, BNP, high-sensitive cardiac troponin T (hs-cTnT), and/or cTnT in blood, plasma, or serum of the subject having, or at risk for, heart failure

[0216] Embodiment 97. The method or use of any one of embodiments 1-93, wherein such method or use ameliorates at least one symptom of heart failure selected from fatigue, rapid or irregular heartbeat, palpitation, shortness of breath, chest pain, dizziness, weakness, dyspnea, orthopnea, edema, hepatic congestion, or ascites in the subject having, or at risk for, heart failure.

[0217] Embodiment 98. The method or use of any one of embodiments 1-93, wherein such method or use slows or prevents progression of one or more symptoms or signs of heart failure in the subject having, or at risk for, heart failure.

[0218] Embodiment 99. The method or use of any one of embodiments 1-93, wherein such method or use improves or eliminates one or more symptoms or signs of heart failure in the subject having, or at risk for, heart failure.

[0219] Embodiment 100. The method or use of any one of embodiments 1-99, wherein the oligomeric compound or salt thereof is administered in a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

[0220] Embodiment 101. The method or use of embodiment 100, wherein the pharmaceutical composition comprises water, saline, or 2mM phosphate buffered isotonic saline, pH 7.4.

[0221] Embodiment 102. The method or use of any one of embodiments 1-101, wherein the oligomeric compound or salt thereof, or pharmaceutical composition is administered parenterally.

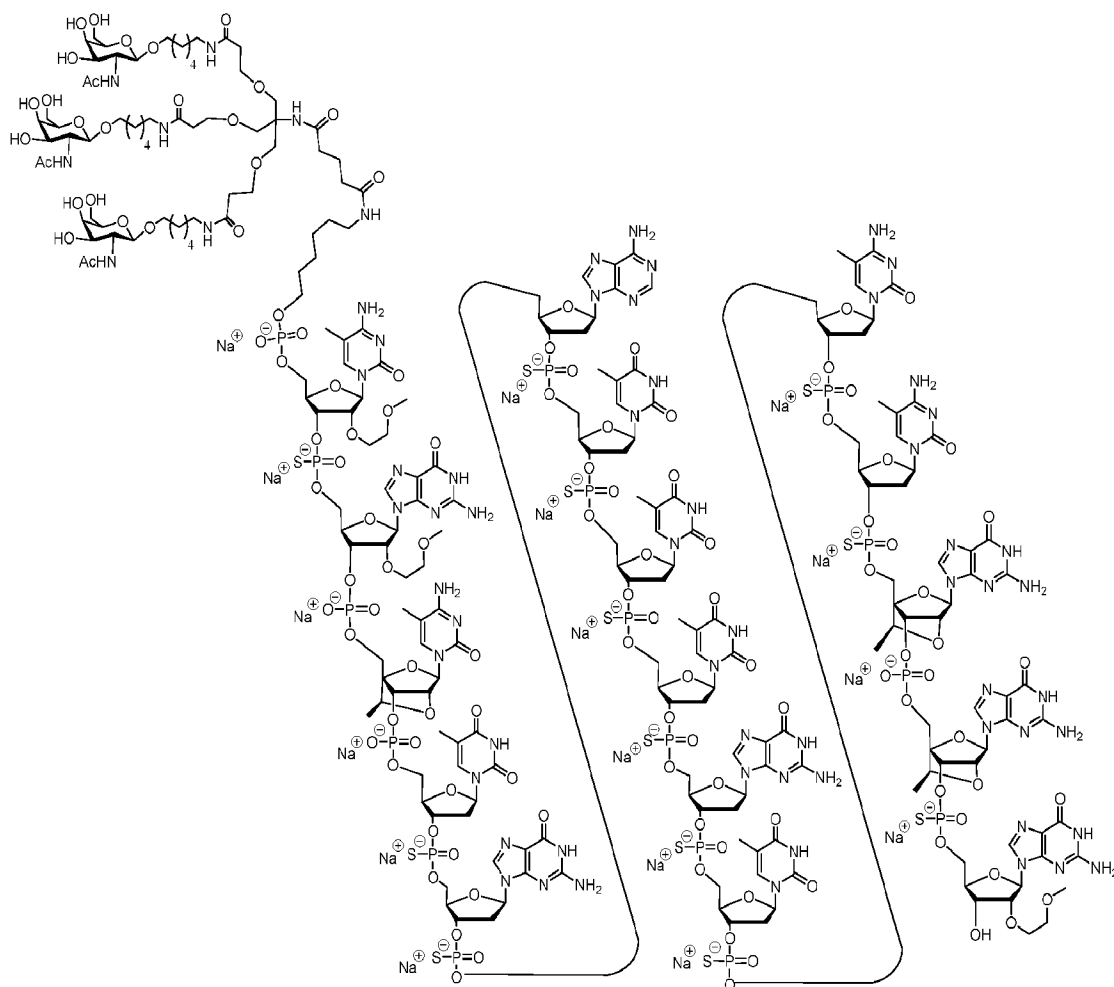
[0222] Embodiment 103. The method or use of embodiment 102, wherein the oligomeric compound or salt thereof, or pharmaceutical composition is administered subcutaneously.

[0223] Embodiment 104. The method or use of embodiment 103 wherein the oligomeric compound or salt thereof, or pharmaceutical composition is administered by a syringe.

[0224] Embodiment 105. The method or use of embodiment 103, wherein the oligomeric compound or salt thereof, or pharmaceutical composition is administered by an autoinjector device.

[0225] Embodiment 106. A method of treating heart failure in a subject, comprising administering a

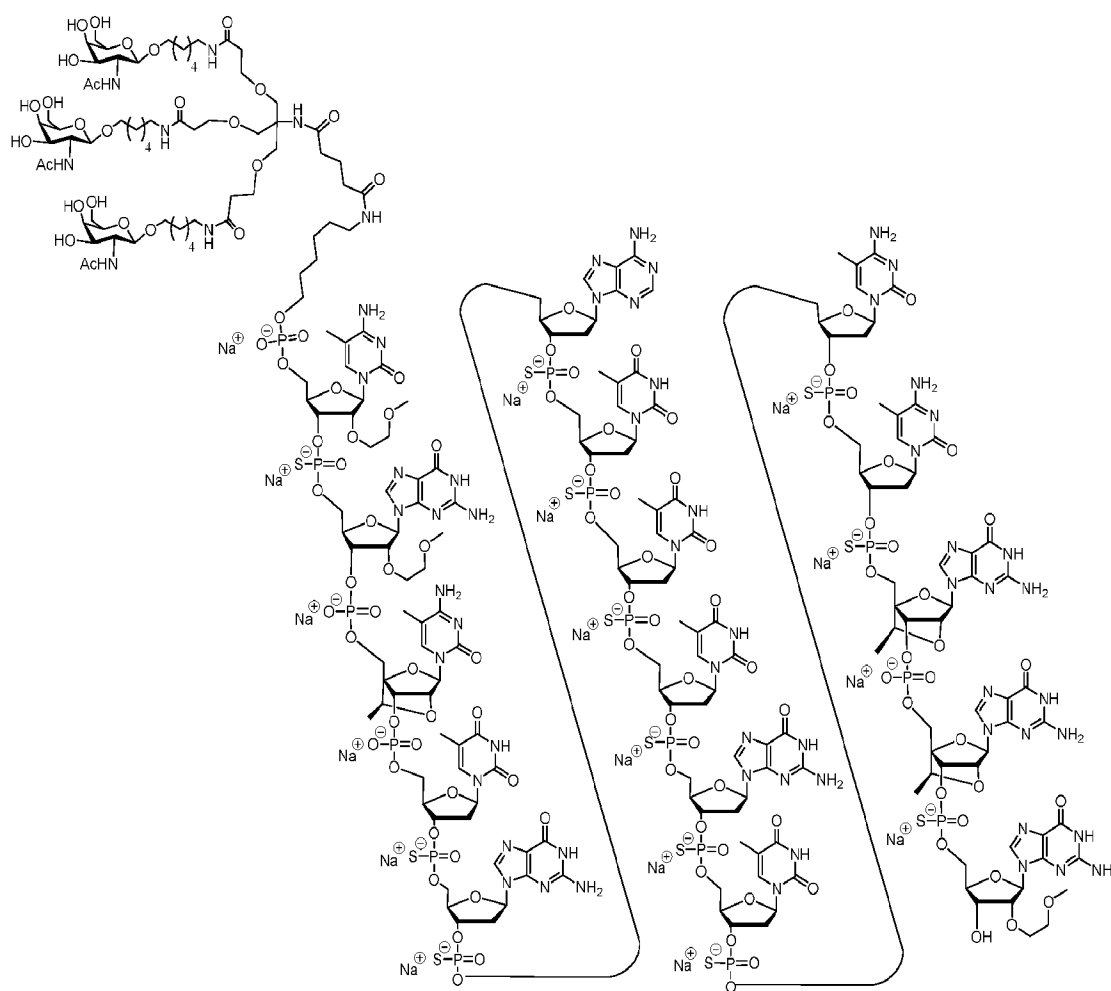
fixed dose of 55 mg to 100 mg of an oligomeric compound or a salt thereof to a subject; wherein administering the oligomeric compound results in amelioration of one or more symptoms and/or lack of progression of heart failure; wherein the oligomeric compound is represented by the following sodium salt:



(SEQ ID NO: 5),

wherein the oligomeric compound is formulated with a pharmaceutically acceptable carrier or excipient selected from sterile water or sterile saline or phosphate buffered saline, formulated for parenteral administration.

[0226] Embodiment 107. Use of a fixed dose of 55 mg to 100 mg of an oligomeric compound or a salt thereof for reducing AGT RNA and/or AGT protein in a subject intolerant, or at risk of being intolerant, to treatment with a renin-angiotensin-aldosterone system (RAAS) inhibitor; wherein the oligomeric compound is compound represented by the following sodium salt:



(SEQ ID NO: 5), and

wherein the oligomeric compound is formulated with a pharmaceutically acceptable carrier or excipient selected from sterile water or sterile saline or phosphate buffered saline, formulated for parenteral administration.

[0227] Embodiment 108. The method of embodiment 106 or the use of embodiment 107, wherein the fixed dose is formulated for subcutaneous administration and contained in a single use vial, pre-filled syringe or an autoinjector device.

[0228] Embodiment 109. A unit dose comprising 50 mg to 200 mg of an oligomeric compound comprising a GalNAc-conjugated modified oligonucleotide represented by the following chemical notation (5' to 3'): ${}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 4) or a salt thereof; wherein:

A = an adenine nucleobase,

${}^m\text{C}$ = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

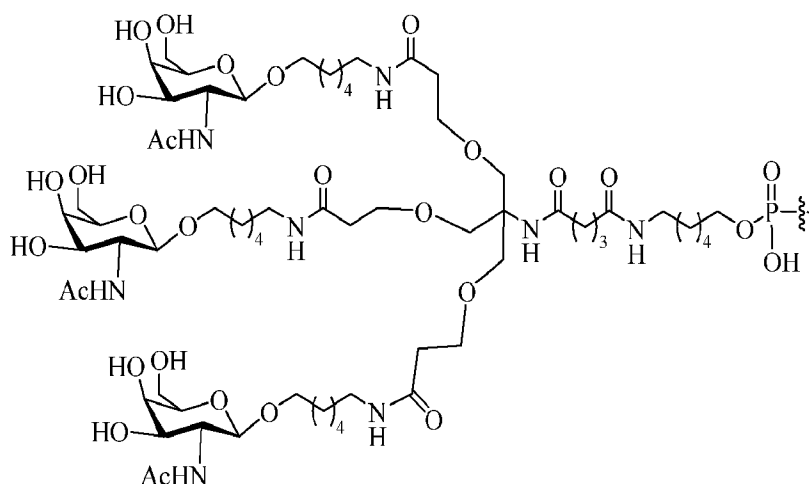
T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 k = a cEt sugar moiety,
 d = an unmodified DNA sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage;

and wherein GalNAc is an N-acetyl galactosamine conjugate moiety.

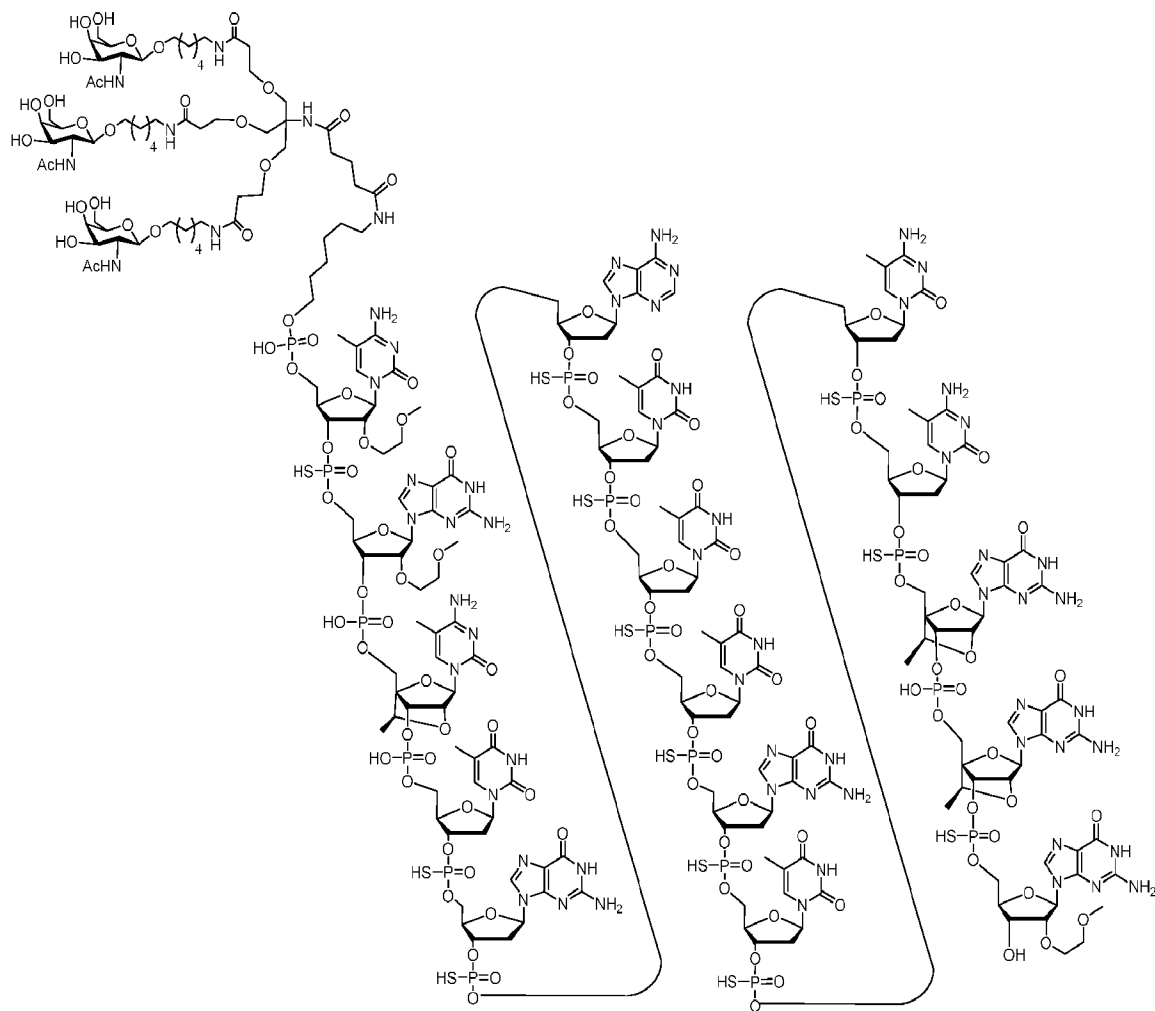
[0229] Embodiment 110. A unit dose comprising 50 mg to 150 mg of an oligomeric compound represented by the following chemical notation (5' to 3'):

THA-C6-GalNAc₃-^mC_{es}G_{eo}^mC_{ko}T_{ds}G_{ds}A_{ds}T_{ds}T_{ds}T_{ds}G_{ds}T_{ds}^mC_{ds}^mC_{ds}G_{ko}G_{ks}G_e (SEQ ID NO: 5) or a salt thereof; 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,
 k = a cEt sugar moiety,
 d = an unmodified DNA sugar moiety,
 s = a phosphorothioate internucleoside linkage,
 o = a phosphodiester internucleoside linkage, and
 THA-C6-GalNAc₃=

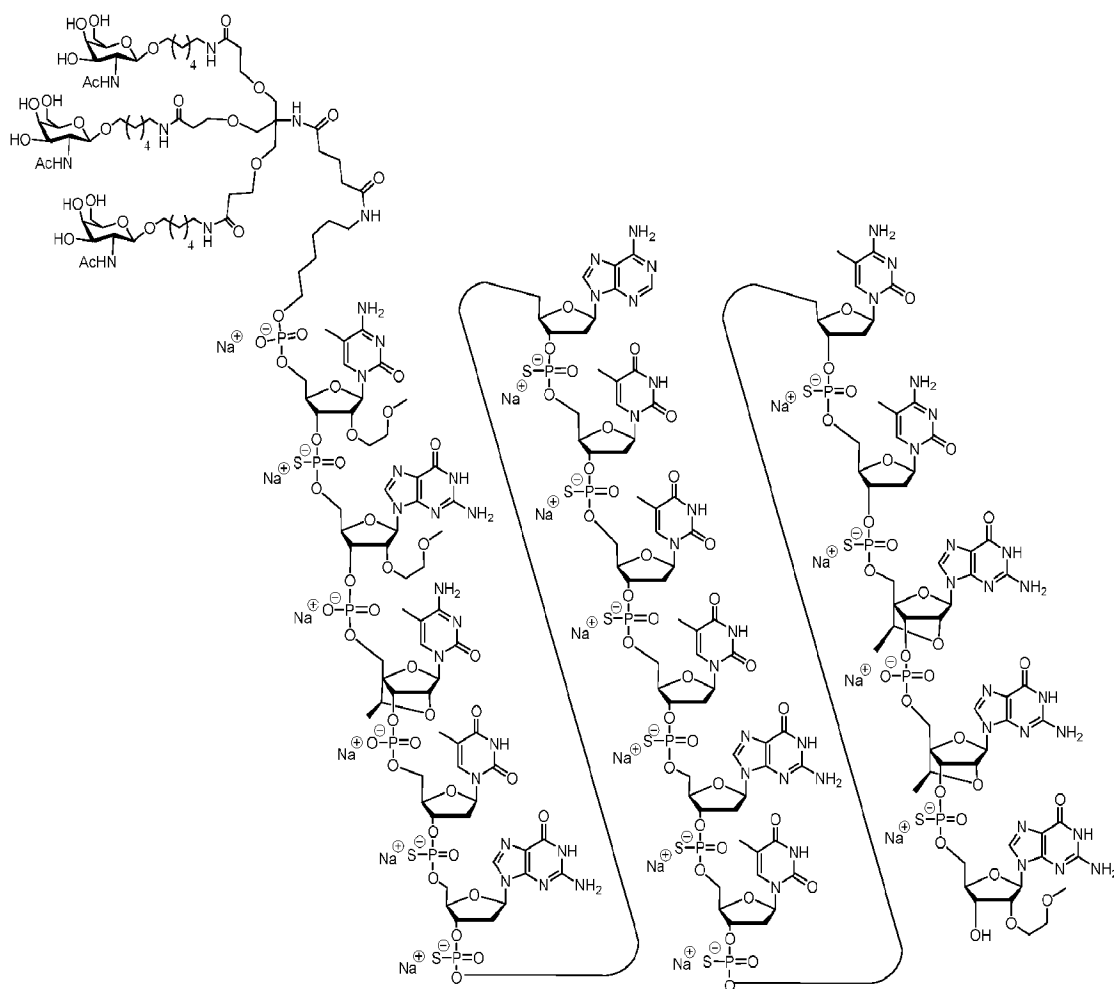


[0230] Embodiment 111. A unit dose comprising 50 mg to 150 mg of an oligomeric compound represented by the following Structure 1:



or a salt thereof.

[0231] Embodiment 112. A unit dose comprising 50 mg to 150 mg an oligomeric compound represented by the following sodium salt Structure 2:



(SEQ ID NO: 5).

[0232] Embodiment 113: The unit dose of any one of embodiments 109-112, comprising an amount of the oligomeric compound or salt thereof within the range of about 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 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 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 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 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 150 mg, 100 mg to 140 mg, 100 mg to 120 mg, 100 mg to 110 mg, 110 mg to 150 mg, 110 mg to 140 mg, 110 mg to 130 mg, 110 mg to 120 mg, 120 mg to 150 mg, 120 mg to 140 mg, 120 mg to 130 mg, 130 mg to 150 mg, 130 mg to 140 mg, 140 mg to 150 mg, 55 mg to 125 mg, 55 mg to 115 mg, 55 mg to 105 mg, 55 mg to 95 mg, 55 mg to 85 mg, 55 mg to 75 mg, 55 mg to 65 mg, 65 mg to 125 mg, 65 mg to 115 mg, 65 mg to 105 mg, or 65 mg to 95 mg, 65 mg to 85 mg, 65 mg to 75 mg, 75 mg to 125 mg, 75 mg to 115 mg,

75 mg to 105 mg, 75 mg to 95 mg, 75 mg to 85 mg, 85 mg to 125 mg, 85 mg to 115 mg, 85 mg to 105 mg, or 85 mg to 95 mg.

[0233] Embodiment 114: The unit dose of any one of embodiments 109-112, comprising an amount of the oligomeric compound or salt thereof within the range of about 50 mg to about 150 mg, about 50 mg to about 140 mg, about 50 mg to about 120 mg, about 50 mg to about 110 mg, about 50 mg to about 100 mg, about 50 mg to about 80 mg, about 50 mg to about 70 mg, about 50 mg to about 60 mg, about 60 mg to about 150 mg, about 60 mg to about 140 mg, about 60 mg to about 120 mg, about 60 mg to about 110 mg, about 60 mg to about 100 mg, about 60 mg to about 80 mg, about 60 mg to about 70 mg, about 70 mg to about 150 mg, about 70 mg to about 140 mg, about 70 mg to about 120 mg, about 70 mg to about 110 mg, about 70 mg to about 100 mg, about 70 mg to about 80 mg, about 80 mg to about 150 mg, about 80 mg to about 140 mg, about 80 mg to about 120 mg, about 80 mg to about 110 mg, about 80 mg to about 100 mg, about 80 mg to about 90 mg, about 90 mg to about 150 mg, about 90 mg to about 140 mg, about 90 mg to about 120 mg, about 90 mg to about 110 mg, about 90 mg to about 100 mg, about 100 mg to about 150 mg, about 100 mg to about 140 mg, about 100 mg to about 120 mg, about 100 mg to about 110 mg, about 110 mg to about 150 mg, about 110 mg to about 140 mg, about 110 mg to about 130 mg, about 110 mg to about 120 mg, about 120 mg to about 150 mg, about 120 mg to about 140 mg, about 120 mg to about 130 mg, about 130 mg to about 150 mg, about 130 mg to about 140 mg, about 140 mg to about 150 mg, about 55 mg to about 125 mg, about 55 mg to about 115 mg, about 55 mg to about 105 mg, about 55 mg to about 95 mg, about 55 mg to about 85 mg, about 55 mg to about 75 mg, about 55 mg to about 65 mg, about 65 mg to about 125 mg, about 65 mg to about 115 mg, about 65 mg to about 105 mg, or about 65 mg to about 95 mg, about 65 mg to about 85 mg, about 65 mg to about 75 mg, about 75 mg to about 125 mg, about 75 mg to about 115 mg, about 75 mg to about 105 mg, about 75 mg to about 95 mg, about 75 mg to about 85 mg, about 85 mg to about 125 mg, about 85 mg to about 115 mg, about 85 mg to about 105 mg, or about 85 mg to about 95 mg.

[0234] Embodiment 115. The unit dose of any one of embodiments 109-112, comprising at least about 50 mg and less than about 150 mg, at least about 50 mg and less than about 145 mg, at least about 50 mg and less than about 140 mg, at least about 50 mg and less than about 135 mg, at least about 50 mg and less than about 130 mg, at least about 50 mg and less than about 125 mg, at least about 50 mg and less than about 120 mg, at least about 50 mg and less than about 115 mg, at least about 50 mg and less than about 110 mg, at least about 50 mg and less than about 105 mg, at least

about 50 mg and less than about 100 mg, at least about 50 mg and less than about 95 mg, at least about 50 mg and less than about 90 mg, at least about 50 mg and less than about 85 mg, at least about 50 mg and less than about 80 mg, at least about 50 mg and less than about 75 mg, at least about 50 mg and less than about 70 mg, at least about 50 mg and less than about 65 mg, at least about 55 mg and less than about 65 mg, at least about 60 mg and less than about 150 mg, at least about 60 mg and less than about 145 mg, at least about 60 mg and less than about 140 mg, at least about 60 mg and less than about 135 mg, at least about 60 mg and less than about 130 mg, at least about 60 mg and less than about 125 mg, at least about 60 mg and less than about 120 mg, at least about 60 mg and less than about 115 mg, at least about 60 mg and less than about 110 mg, at least about 60 mg and less than about 105 mg, at least about 60 mg and less than about 100 mg, at least about 60 mg and less than about 95 mg, at least about 70 mg and less than about 150 mg, at least about 70 mg and less than about 145 mg, at least about 70 mg and less than about 140 mg, at least about 70 mg and less than about 135 mg, at least about 70 mg and less than about 130 mg, at least about 70 mg and less than about 125 mg, at least about 70 mg and less than about 120 mg, at least about 70 mg and less than about 115 mg, at least about 70 mg and less than about 110 mg, at least about 70 mg and less than about 105 mg, at least about 70 mg and less than about 100 mg, at least about 70 mg and less than about 95 mg, at least about 80 mg and less than about 150 mg, at least about 80 mg and less than about 145 mg, at least about 80 mg and less than about 140 mg, at least about 80 mg and less than about 135 mg, at least about 80 mg and less than about 130 mg, at least about 80 mg and less than about 125 mg, at least about 80 mg and less than about 120 mg, at least about 80 mg and less than about 115 mg, at least about 80 mg and less than about 110 mg, at least about 80 mg and less than about 105 mg, at least about 80 mg and less than about 100 mg, at least about 80 mg and less than about 95 mg, or at least about 85 mg and less than about 95 mg of the oligomeric compound or salt thereof.

[0235] Embodiment 116. The unit dose of any one of embodiments 109-112, comprising 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, or about 150 mg of the oligomeric compound or salt thereof.

[0236] Embodiment 117. The unit dose of any one of embodiments 109-112, comprising 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, or 150 mg of the oligomeric compound or salt thereof.

[0237] Embodiment 118. The unit dose of any one of embodiments 109-112, comprising about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, or about 100 mg of the oligomeric compound or salt thereof.

[0238] Embodiment 119. The unit dose of any one of embodiments 109-112, comprising 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, or 100 mg of the oligomeric compound or salt thereof.

[0239] Embodiment 120. The unit dose of any one of embodiments 109-112, comprising an amount of the oligomeric compound or salt thereof within the range of about 55 mg to about 100 mg, about 60 mg to about 100 mg, about 65 mg to about 100 mg, about 70 mg to about 100 mg, about 75 mg to about 100 mg, about 80 mg to about 100 mg, about 85 mg to about 100 mg, about 85 mg to about 100 mg, or about 85 mg to about 95 mg.

[0240] Embodiment 121. The unit dose of any one of embodiments 109-112, comprising about 55 mg of the oligomeric compound or salt thereof.

[0241] Embodiment 122. The unit dose of any one of embodiments 109-112, comprising about 60 mg of the oligomeric compound or salt thereof.

[0242] Embodiment 123. The unit dose of any one of embodiments 109-112, comprising about 65 mg of the oligomeric compound or salt thereof.

[0243] Embodiment 124. The unit dose of any one of embodiments 109-112, comprising about 70 mg of the oligomeric compound or salt thereof.

[0244] Embodiment 125. The unit dose of any one of embodiments 109-112, comprising about 75 mg of the oligomeric compound or salt thereof.

[0245] Embodiment 126. The unit dose of any one of embodiments 109-112, comprising about 80 mg of the oligomeric compound or salt thereof.

[0246] Embodiment 127. The unit dose of any one of embodiments 109-112, comprising about 85 mg of the oligomeric compound or salt thereof.

[0247] Embodiment 128. The unit dose of any one of embodiments 109-112, comprising about 90 mg of the oligomeric compound or salt thereof.

[0248] Embodiment 129. The unit dose of any one of embodiments 109-112, comprising about 95 mg of the oligomeric compound or salt thereof.

[0249] Embodiment 130. The unit dose of any one of embodiments 109-112, comprising about 100 mg of the oligomeric compound or salt thereof.

[0250] Embodiment 131. The unit dose of any one of embodiments 109-112, comprising 55 mg to 95 mg of the oligomeric compound or salt thereof.

[0251] Embodiment 132. The unit dose of any one of embodiments 109-131, further comprising a neprilysin inhibitor.

[0252] Embodiment 133. The unit dose of embodiment 132, wherein the neprilysin inhibitor is sacubitril.

[0253] Embodiment 134. The unit dose of any one of embodiments 109-133, further comprising an ACEi, ARB, ARNi or MRA.

[0254] Embodiment 135. The unit dose of any embodiment 132 or embodiment 133, further comprising an ARB which is valsartan.

[0255] Embodiment 136. The unit dose of embodiment 134 or embodiment 135, wherein the dose of the ACEi, ARB, ARNi or MRA is lower than the Guideline-recommended, target dose for treating HFrEF.

[0256] Embodiment 137. The unit dose of embodiment 136, wherein the dose of the ACEi, ARB, ARNi or MRA is less than about 80%, 70%, 60%, 55%, 50%, 45%, or 40% of the Guideline-recommended target dose for treating HFrEF.

[0257] Embodiment 138. The unit dose of any one of embodiments 109-131, wherein the unit dose does not contain any other RAAS inhibitor.

[0258] Embodiment 139. The unit dose of any one of embodiments 109-138, further comprising a pharmaceutically acceptable carrier, adjuvant or excipient.

[0259] Embodiment 140. The unit dose of embodiments 139, consisting of the oligomeric compound or salt thereof and a pharmaceutically acceptable carrier or excipient.

[0260] Embodiment 141. The unit dose of embodiment 139, wherein the pharmaceutically acceptable carrier or excipient is sterile water or sterile saline or phosphate buffered saline.

[0261] Embodiment 142. The unit dose of embodiment 141, consisting of the oligomeric compound or salt thereof and sterile water or sterile saline or phosphate buffered saline.

[0262] Embodiment 143. The unit dose of any one of embodiments 109-142, formulated for parenteral administration.

[0263] Embodiment 144. The unit dose of embodiment 143, formulated for subcutaneous, intramuscular, or intravenous administration.

[0264] Embodiment 145. The unit dose of embodiment 143, formulated for subcutaneous administration.

[0265] Embodiment 146. The unit dose of any one of embodiments 109-145, contained in a single-dose vial.

[0266] Embodiment 147. The unit dose of any one of embodiments 109-145, provided in multi-dose vials.

[0267] Embodiment 148. The unit dose of any one of embodiments 109-145, contained in a prefilled syringe.

[0268] Embodiment 149. The unit dose of any one of embodiments 109-145, contained in a single-dose prefilled syringe.

[0269] Embodiment 150. The unit dose of any one of embodiments 109-145, contained in an autoinjector device.

[0270] Embodiment 151. A kit, comprising:

- (a) the unit dose of any one of embodiments 109-150, and
- (b) instructions for use, and, optionally,
- (c) means for administering the unit dose.

[0271] Embodiment 152. The kit of embodiment 151, wherein the instructions are for use in reducing the amount of AGT RNA and/or AGT protein in a subject having or at risk for heart failure.

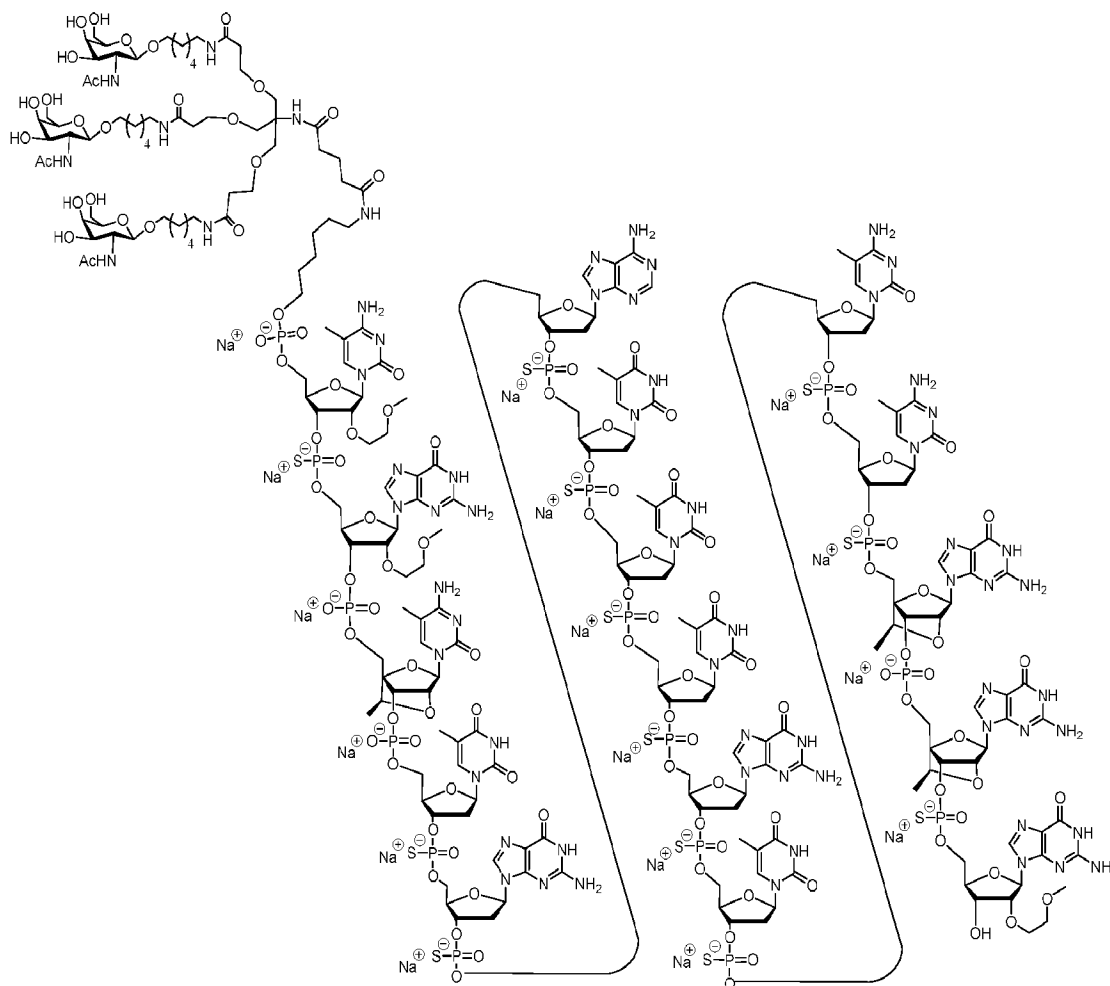
[0272] Embodiment 153. The kit of embodiment 151, wherein the instructions are for use in treating, or ameliorating one or more symptoms of, heart failure in a subject having or at risk for heart failure.

[0273] Embodiment 154. The method or use or unit dose of any one of embodiments 1-153, wherein the modified oligonucleotide is single-stranded.

[0274] Embodiment 155. The method or use or unit dose of any one of embodiments 1-153, wherein the modified oligonucleotide is the only oligonucleotide in the oligomeric compound.

[0275] Embodiment 156. The method or use or unit dose of any one of embodiments 1-153, wherein the modified oligonucleotide is double-stranded.

[0276] Embodiment 157. A unit dose comprising 55 mg to 100 mg of an oligomeric compound represented by the following sodium salt:



(SEQ ID NO: 5), and

a pharmaceutically acceptable carrier or excipient selected from sterile water or sterile saline or phosphate buffered saline, formulated for parenteral administration.

[0277] Embodiment 158. The unit dose of embodiment 157, formulated for subcutaneous administration and contained in a single use vial, pre-filled syringe or an autoinjector device.

[0278] Embodiment 159. A method for reducing the amount of angiotensinogen (AGT) RNA and/or AGT protein in a subject who is or is at risk of being intolerant to treatment with a renin-angiotensin-aldosterone system (RAAS) inhibitor, comprising administering about 15 mg to about 200 mg of an oligomeric agent or salt thereof to a subject having or at risk for heart failure, wherein the oligomeric agent comprises a modified oligonucleotide consisting of 16-30 linked nucleosides, and wherein the modified oligonucleotide comprises a nucleobase sequence of at least 16 contiguous

nucleosides at least 80% complementary to the nucleobase sequence of an equal length region of nucleobases 2046-2061 of SEQ ID NO: 1 or nucleobases 14940-14955 of SEQ ID NO: 2; wherein:

the amount of AGT RNA and/or AGT protein in the subject is decreased by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent.

[0279] Embodiment 160. A method of treating heart failure in a subject having or at risk for heart failure who is or is at risk of being intolerant to treatment with a renin-angiotensin-aldosterone system (RAAS) inhibitor, comprising administering about 15 mg to about 200 mg of an oligomeric agent or salt thereof to a subject having or at risk for heart failure, wherein the oligomeric agent comprises a modified oligonucleotide consisting of 16-30 linked nucleosides, and wherein the modified oligonucleotide comprises a nucleobase sequence of at least 16 contiguous nucleosides at least 80% complementary to the nucleobase sequence of an equal length region of nucleobases 2046-2061 of SEQ ID NO: 1 or nucleobases 14940-14955 of SEQ ID NO: 2; and wherein the amount of AGT RNA and/or AGT protein in the subject is decreased by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent.

[0280] Embodiment 161. A method for reducing AGT RNA and/or AGT protein in a subject, comprising administering 60 mg to 120 mg of an oligomeric agent or salt thereof to a subject having or at risk for heart failure with reduced ejection fraction (HFrEF); wherein the oligomeric agent comprises a modified oligonucleotide consisting of 16-30 linked nucleosides, and wherein the modified oligonucleotide comprises a nucleobase sequence of at least 16 contiguous nucleosides at least 80% complementary to the nucleobase sequence of an equal length region of nucleobases 2046-2061 of SEQ ID NO: 1 or nucleobases 14940-14955 of SEQ ID NO: 2; and wherein the amount of AGT RNA and/or AGT protein in the subject is decreased by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent.

[0281] Embodiment 162. Use of an oligomeric agent or salt thereof for treating heart failure in a subject having or at risk for heart failure who is or is at risk of being intolerant to treatment with a renin-angiotensin-aldosterone system (RAAS) inhibitor, wherein:

the oligomeric agent comprises a modified oligonucleotide consisting of 16-30 linked nucleosides and wherein the modified oligonucleotide comprises a nucleobase sequence of at least

16 contiguous nucleosides at least 80% complementary to the nucleobase sequence of an equal length region of nucleobases 2046-2061 of SEQ ID NO: 1 or nucleobases 14940-14955 of SEQ ID NO: 2, or salt thereof to a subject having or at risk for heart failure; and

wherein the oligomeric agent decreases the amount of AGT RNA and/or AGT protein in a subject by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent.

[0282] Embodiment 163. Use of an oligomeric agent or salt thereof in the manufacture of a medicament for reducing the amount of AGT RNA and/or AGT protein in a subject or for treating heart failure and/or ameliorating one or more symptoms of heart failure, wherein:

[0283] the oligomeric agent comprises a modified oligonucleotide consisting of 16-50 linked nucleosides, wherein the modified oligonucleotide comprises at least 13 contiguous nucleosides at least 80% complementary to the nucleobase sequence of an equal length region of nucleobases 2046-2061 of SEQ ID NO: 1 or nucleobases 14940-14955 of SEQ ID NO: 2; and

[0284] the oligomeric agent decreases the amount of AGT RNA and/or AGT protein in a subject by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent or salt thereof.

[0285] Embodiment 164. Use of 60 mg to 120 mg of an oligomeric agent or a salt thereof for reducing AGT RNA and/or AGT protein in a subject having or at risk for heart failure with reduced ejection fraction (HFrEF); wherein the oligomeric agent comprises a modified oligonucleotide consisting of 16-30 linked nucleosides, and wherein the modified oligonucleotide comprises a nucleobase sequence of at least 16 contiguous nucleosides at least 80% complementary to the nucleobase sequence of an equal length region of nucleobases 2046-2061 of SEQ ID NO: 1 or nucleobases 14940-14955 of SEQ ID NO: 2; and wherein the amount of AGT RNA and/or AGT protein in the subject is decreased by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent.

[0286] Embodiment 165. The method or use of any one of embodiments 159-164, wherein the subject has or is at risk for, or the heart failure is, heart failure with reduced ejection fraction

(HFrfEF), heart failure with mid-range ejection fraction (HFmrEF), heart failure with improved ejection fraction (HFimpEF), or heart failure with preserved ejection fraction (HFpEF).

[0287] Embodiment 166. The method or use of any one of embodiments 159-164, wherein the subject has a left ventricular ejection fraction of about 50% or less, about 40% or less, or about 35% or less, or about 30% or less.

[0288] Embodiment 167. The method or use of any one of embodiments 159-164, wherein the subject has one or more of asymptomatic left ventricular dysfunction (ALVD), asymptomatic or symptomatic valvular heart disease, left ventricular hypertrophy, left ventricular fibrosis, left ventricular dilatation, and left ventricular hypocontractility.

[0289] Embodiment 168. The method or use of any one of embodiments 159-167, wherein the amount of AGT protein in the liver of the subject is reduced.

[0290] Embodiment 169. The method or use of any one of embodiments 159-167, wherein the amount of AGT protein in the blood, serum or plasma of the subject is reduced.

[0291] Embodiment 170. The method or use of any one of embodiments 159-169, wherein a decrease in the amount of AGT RNA and/or AGT protein in the subject is less than 95%, or less than 94%, or less than 93%, or less than 92%, or less than 91%, or less than 90% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent or salt thereof.

[0292] Embodiment 171. The method or use of any one of embodiments 159-169, wherein the amount of AGT RNA and/or AGT protein in the subject is decreased by no more than 85%, or no more than 86%, or no more than 87%, or no more than 88%, or no more than 89%, or no more than 90%, or no more than 91%, or no more than 92%, or no more than 93%, or no more than 94%, or no more than 95% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent or salt thereof.

[0293] Embodiment 172. The method or use of any one of embodiments 159-169, wherein the amount of AGT RNA and/or AGT protein is decreased by at least 75%, at least 80% or at least 85% and less than 95% compared to the amount of AGT protein prior to administering the oligomeric agent or salt thereof.

[0294] Embodiment 173. The method or use of any one of embodiments 159-169, wherein the amount of AGT RNA and/or AGT protein is decreased by at least 70% or at least 75%, at least 80%

or at least 85% and less than 90% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent or salt thereof.

[0295] Embodiment 174. The method or use of any one of embodiments 159-169, wherein the amount of AGT RNA and/or AGT protein in the subject is decreased by at least 70% or at least 75% and less than 95%, less than 94%, less than 93%, less than 92%, less than 91%, less than 90%, less than 89%, less than 88%, or less than 85% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent or salt thereof.

[0296] Embodiment 175. The method or use of any one of embodiments 159-174, wherein the nucleobase sequence comprises at least 13, at least 14, at least 15 or at least 16 contiguous nucleobases at least 85%, at least 90%, at least 95%, or 100% complementary to the nucleobase sequence of an equal length region of nucleobases 2046-2061 of SEQ ID NO: 1 or nucleobases 14940-14955 of SEQ ID NO: 2.

[0297] Embodiment 176. The method or use of any one of embodiments 159-174, wherein the nucleobase sequence comprises at least 13, at least 14, at least 15, or at least 16 contiguous nucleobases of any one of the nucleobase sequence of SEQ ID NOs: 3-5.

[0298] Embodiment 177. The method or use of any one of embodiments 159-174, wherein the modified oligonucleotide consists of 16 to 17, 16 to 18, 16 to 20, 16 to 25, 16 to 30, 17 to 20, 17 to 25, 17 to 30, 18 to 20, 18 to 25, 18 to 30, 19 to 20, 19 to 25, 19 to 30, 20 to 25, 20 to 30, 21-23, 21 to 25, 21 to 30, 22 to 25, 22 to 30, 23 to 25, or 23 to 30 linked nucleosides.

[0299] Embodiment 178 The method or use of any one of embodiments 159-174, wherein the modified oligonucleotide consists of 16 to 30 linked nucleosides and comprises or consists of a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 3-5.

[0300] Embodiment 179. The method or use of any one of embodiments 159-178, wherein the modified oligonucleotide comprises one or more i) modified nucleosides comprising a modified sugar moiety, ii) cyclic sugar surrogate, iii) acyclic sugar surrogate, iii) modified internucleoside linkage, and/or iv) modified nucleobase.

[0301] Embodiment 180. The method or use of embodiment 179, wherein the modified sugar moiety is a modified furanosyl sugar moiety or a sugar surrogate.

[0302] Embodiment 181. The method or use of embodiment 179, wherein the modified nucleoside comprises a bicyclic modified sugar moiety comprising a 4'-2' bridge selected from 4'-CH₂-O-2' and 4'-CH(CH₃)-O-2'.

[0303] Embodiment 182. The method or use of embodiment 179, wherein the modified nucleoside comprises a non-bicyclic modified sugar moiety selected from a 2'-MOE sugar moiety, 2'-OMe sugar moiety, a 2'-F sugar moiety, or a 2'-NMA sugar moiety.

[0304] Embodiment 183. The method or use of embodiment 179, wherein each internucleoside linkage of the modified oligonucleotide is independently selected from a phosphodiester internucleoside linkage, a phosphorothioate internucleoside linkage, and a mesyl phosphoramidate internucleoside.

[0305] Embodiment 184. The method or use of embodiment 179, wherein the modified nucleobase is 5-methylcytosine or hypoxanthine.

[0306] Embodiment 185. The method or use of embodiment 179, wherein each nucleoside of the modified oligonucleotide comprises a nucleobase.

[0307] Embodiment 186. The method or use of embodiment 179, wherein each nucleoside of the modified oligonucleotide is independently selected from a furanosyl nucleoside, a cyclic sugar surrogate nucleoside, and an acyclic sugar surrogate nucleoside comprising a nucleobase.

[0308] Embodiment 187. The method or use of embodiment 179, wherein at least one nucleoside of the modified oligonucleotide comprises an unmodified sugar moiety.

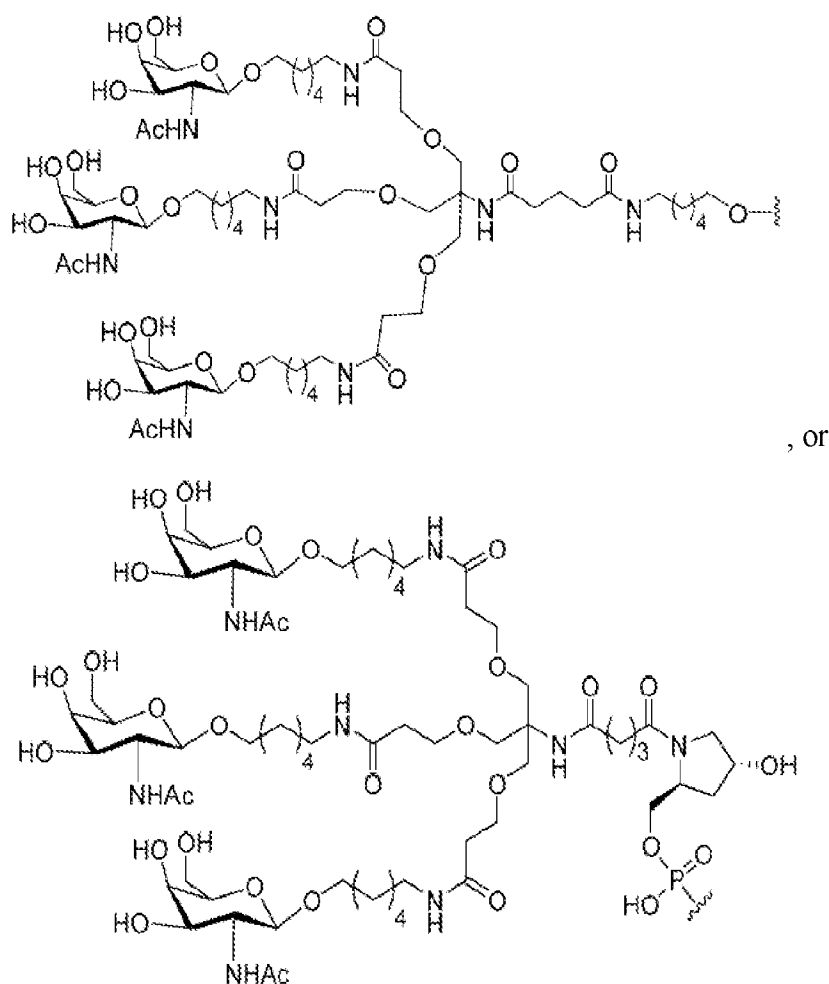
[0309] Embodiment 188. The method or use of embodiment 179, wherein at least one nucleoside of the modified oligonucleotide comprises an unmodified DNA sugar moiety.

[0310] Embodiment 189. The method or use of any one of embodiments 1-188, wherein the oligomeric agent or salt thereof comprises a conjugate group comprising a conjugate linker and a conjugate moiety comprising a cell-targeting moiety.

[0311] Embodiment 190. The method or use of embodiment 189, wherein the cell-targeting moiety comprises a moiety that interacts with or binds to a liver cell.

[0312] Embodiment 191. The method or use of embodiment 190, wherein the conjugate group comprises a N-acetyl galactosamine (GalNAc) moiety.

[0313] Embodiment 192. The method or use of embodiment 191, wherein the conjugate group comprises the following structure:



[0314] Embodiment 193. The method or use of any one of embodiments 189-192, wherein the conjugate group comprises a conjugate linker consisting of a single bond and/or comprises a cleavable linker.

[0315] Embodiment 194. The method or use of any one of embodiments 189-193, wherein the conjugate group is attached to the 5'-terminal nucleoside or to the 3'-terminal nucleoside of the modified oligonucleotide.

[0316] Embodiment 195. The method or use of any one of embodiments 159-194, wherein the modified oligonucleotide comprises a deoxy region consisting of 5-12 linked nucleosides.

[0317] Embodiment 196. The method or use of embodiment 195, wherein the deoxy region consists of 6, 7, 8, 9, 10, or 6-10 linked nucleosides.

[0318] Embodiment 197. The method or use of embodiment 195 or embodiment 196, wherein each nucleoside immediately adjacent to the deoxy region comprises a modified sugar moiety.

[0319] Embodiment 198. The method or use of embodiment 196, wherein the deoxy region is flanked on the 5'-side by a 5'-region consisting of 1-6 nucleosides and on the 3'-side by a 3'-region consisting of 1-6 linked nucleosides; wherein the 3'-most nucleoside of the 5'-region comprises a modified sugar moiety and the 5'-most nucleoside of the 3'-region comprises a modified sugar moiety.

[0320] Embodiment 199. The method or use of embodiment 198, wherein each nucleoside of the 3'-region comprises a modified sugar moiety and/or wherein each nucleoside of the 5'-region comprises a modified sugar moiety.

[0321] Embodiment 200. The method or use of any one of embodiments 199, wherein each nucleoside of the 5'-region independently is a cEt nucleoside, a 2'-OMe nucleoside, or a 2'-MOE nucleoside and each nucleoside of the 3'-region independently is a cEt nucleoside, a 2'-OMe nucleoside, or a 2'-MOE nucleoside.

[0322] Embodiment 201. The method or use of any one of embodiments 195-200, wherein the modified oligonucleotide has a 5'-region consisting of 3 linked nucleosides, a deoxy region consisting of 6-10 linked nucleosides, and a 3'-region consisting of 1-6 linked nucleosides.

[0323] Embodiment 202. The method or use of any one of embodiments 195-200, wherein the modified oligonucleotide has a sugar motif (5' to 3') selected from: eekdddddddddkke, ekkdddddddddkke, kkkdydddddddkkk, kkkddydddddddkkk, kkkdddydddddddkkk, kkkdddddyydddddddkkk, or eeeeeeeeeeeeeee; wherein 'e' represents a 2'-MOE sugar moiety, 'k' represents a cEt sugar moiety, 'd' represents an unmodified DNA sugar moiety, and 'y' represents a 2'-OMe sugar moiety.

[0324] Embodiment 203. The method or use of any one of embodiments 159-202, wherein each internucleoside linkage of the modified oligonucleotide is independently selected from a phosphodiester internucleoside linkage and a phosphorothioate internucleoside linkage.

[0325] Embodiment 204. The method or use of any one of embodiments 159-202, wherein the modified oligonucleotide has an internucleoside linkage motif of soosssssssos; wherein s is a phosphorothioate internucleoside linkage and o is a phosphodiester internucleoside linkage.

[0326] Embodiment 205. A method for reducing the amount of angiotensinogen (AGT) RNA and/or AGT protein in a subject who is or is at risk of being intolerant to treatment with a renin-angiotensin-aldosterone system (RAAS) inhibitor, comprising administering about 15 mg to about 200 mg an oligomeric agent or salt thereof to a subject having or at risk for heart failure, wherein the

oligomeric agent comprises a modified oligonucleotide consisting of 16-30 linked nucleosides, and wherein the modified oligonucleotide comprises a nucleobase sequence of at least 16 contiguous nucleosides at least 80% complementary to the nucleobase sequence of an equal length region of SEQ ID NO: 1 or SEQ ID NO: 2;

[0327] wherein: the amount of AGT RNA and/or AGT protein in the subject is decreased by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent; and

[0328] wherein the subject has or is at risk for heart failure with reduced ejection fraction (HFrEF), heart failure with mid-range ejection fraction (HFmrEF), heart failure with improved ejection fraction (HFimpEF), or heart failure with preserved ejection fraction (HFpEF).

[0329] Embodiment 206. A method of treating heart failure in a subject having or at risk for heart failure who is or is at risk of being intolerant to treatment with a renin-angiotensin-aldosterone system (RAAS) inhibitor, comprising administering about 15 mg to about 200 mg of an oligomeric agent or salt thereof to a subject having or at risk for heart failure, wherein the oligomeric agent comprises a modified oligonucleotide consisting of 16-30 linked nucleosides, and wherein the modified oligonucleotide comprises a nucleobase sequence of at least 16 contiguous nucleosides at least 80% complementary to the nucleobase sequence of an equal length region of SEQ ID NO: 1 or SEQ ID NO: 2; and wherein the amount of AGT RNA and/or AGT protein in the subject is decreased by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent; and wherein the subject has or is at risk for heart failure with reduced ejection fraction (HFrEF), heart failure with mid-range ejection fraction (HFmrEF), heart failure with improved ejection fraction (HFimpEF), or heart failure with preserved ejection fraction (HFpEF).

[0330] Embodiment 207. Use of an oligomeric agent or salt thereof for treating heart failure in a subject having or at risk for heart failure who is or is at risk of being intolerant to treatment with a renin-angiotensin-aldosterone system (RAAS) inhibitor, wherein:

[0331] the oligomeric agent comprises a modified oligonucleotide consisting of 16-30 linked nucleosides, wherein the modified oligonucleotide comprises a nucleobase sequence of at least 16 contiguous nucleosides and wherein the modified oligonucleotide is at least 80% complementary to

the nucleobase sequence of an equal length region of SEQ ID NO: 1 or SEQ ID NO: 2, or salt thereof to a subject having or at risk for heart failure; and

[0332] wherein the oligomeric agent decreases the amount of AGT RNA and/or AGT protein in a subject by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent; and wherein the subject has or is at risk for heart failure with reduced ejection fraction (HFrEF), heart failure with mid-range ejection fraction (HFmrEF), heart failure with improved ejection fraction (HFimpEF), or heart failure with preserved ejection fraction (HFpEF).

[0333] Embodiment 208. Use of an oligomeric agent or salt thereof in the manufacture of a medicament for reducing the amount of AGT RNA and/or AGT protein in a subject or for treating heart failure and/or ameliorating one or more symptoms of heart failure, wherein:

[0334] the oligomeric agent comprises a modified oligonucleotide consisting of 12-80 linked nucleosides, wherein the modified oligonucleotide comprises at least 16 contiguous nucleosides at least 80% complementary to the nucleobase sequence of an equal length region of SEQ ID NO: 1 or SEQ ID NO: 2; and

[0335] the oligomeric agent decreases the amount of AGT RNA and/or AGT protein in a subject by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent or salt thereof; and wherein the subject has or is at risk for heart failure with reduced ejection fraction (HFrEF), heart failure with mid-range ejection fraction (HFmrEF), heart failure with improved ejection fraction (HFimpEF), or heart failure with preserved ejection fraction (HFpEF).

[0336] Embodiment 209. A method for reducing AGT RNA and/or AGT protein in a subject, comprising administering 60 mg to 120 mg of an oligomeric agent or salt thereof to a subject having or at risk for heart failure with reduced ejection fraction (HFrEF); wherein the oligomeric agent comprises a modified oligonucleotide consisting of 12-80 linked nucleosides, wherein the modified oligonucleotide comprises at least 16 contiguous nucleosides at least 80% complementary to the nucleobase sequence of an equal length region of SEQ ID NO: 1 or SEQ ID NO: 2; and wherein the oligomeric agent decreases the amount of AGT RNA and/or AGT protein in a subject by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared to the baseline amount

of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent or salt thereof.

[0337] Embodiment 210. Use of 60 mg to 120 mg of an oligomeric agent or a salt thereof for reducing AGT RNA and/or AGT protein in a subject having or at risk for heart failure with reduced ejection fraction (HFrEF); wherein the oligomeric agent comprises a modified oligonucleotide consisting of 12-80 linked nucleosides, wherein the modified oligonucleotide comprises at least 16 contiguous nucleosides at least 80% complementary to the nucleobase sequence of an equal length region of SEQ ID NO: 1 or SEQ ID NO: 2; and wherein the oligomeric agent decreases the amount of AGT RNA and/or AGT protein in a subject by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent or salt thereof.

[0338] A. Angiotensinogen (AGT)

[0339] Angiotensinogen (AGT) has been proposed as a genetic target for treating hypertension and cardiovascular disorders because chronic overactivity of the renin-angiotensin-aldosterone system (RAAS) pathway is a major contributor to the pathogenesis of cardiovascular disorders, including hypertension, chronic kidney disease and heart failure. A representative nucleobase sequence for a human AGT gene (encoding human AGT RNA, wherein angiotensinogen protein is the expression product) is the complement of the nucleotides of GenBank Accession No. NC_000001.11 truncated from nucleotides 230700001 to 230718000 (designated herein as SEQ ID NO: 2). A representative nucleobase sequence for a human AGT RNA is GENBANK Accession No. NM_000029.3 (designated herein as SEQ ID NO: 1). The systemic RAAS cascade begins with renin-mediated cleavage of angiotensinogen (AGT), whose plasma levels are primarily liver derived, to generate angiotensin I, which is converted to the potent vasoactive peptide angiotensin II (Ang II), which mediates vasoconstriction of vascular smooth muscle cells and aldosterone release from the adrenal cortex. The RAAS pathway acts as a key regulator of acute hemodynamic changes in the body and is responsive to decreases in cardiac output that occur during heart failure, but persistent overactivation results in excessive vasoconstriction, salt and water retention, cardiac remodeling and hypertrophy, and fibrosis. Thus, inhibition of the most proximal prohormone in the RAAS pathway is proposed to mitigate effects of RAAS overactivity.

[0340] For instance, methods have been described of treating hypertension by administering antisense oligonucleotides, for example, compound 757456 (also referred to as IONIS-AGT-L_{RX}),

which targets human AGT (see, e.g., WO2017/062816). Several clinical trials of compound 757456 have been conducted to evaluate safety, efficacy in reducing AGT levels, and lowering blood pressure in hypertensive subjects (see, e.g., Morgan et al. (2021) *J Am Coll Cardiol Basic Science* 6(6):485-496). A phase 1 (NCT03101878) and three phase 2 trials of compound 757456 were conducted to evaluate treatment of subjects having controlled hypertension with the compound as a monotherapy (NCT03714776) and treatment of subjects having uncontrolled hypertension with the compound as an add-on therapy to 2-3 antihypertensive medications (NCT04083222) or 3 or more antihypertensive medications (NCT04714320). Results of all four studies of compound 757456 demonstrated safety and tolerability of the compound at single doses up to 80 mg and weekly doses at 80 mg or 120 mg. Results indicated a higher reduction in systolic and diastolic blood pressure (as compared to placebo) that was clinically meaningful (> 5 mmHg) though not statistically significant in studies. The maximum mean reduction in plasma AGT in these trials was 67% as compared to baseline. Another phase 2 trial was conducted to evaluate compound 757456 safety, tolerability and effect of weekly subcutaneous (SC) injection of compound 757456 on plasma AGT concentration in subjects with chronic heart failure with reduced ejection fraction (HFrEF) receiving standard of care therapy (e.g., an ACEi, ARB or sacubitril/valsartan, or a beta-blocker or an MRA) (see Example 1B). No hypotension, hepatic, renal or potassium safety signals were observed in this study, and dose-dependent reductions in plasma AGT were observed in all treated subjects. No significant change in NT-proBNP levels in treatment groups was observed compared to the placebo group, though the study was not powered for significance to detect changes in NT-proBNP. Similar to earlier studies, reduction in plasma AGT was 63% as compared to baseline, and no significant change in blood pressure was observed, though the study was not powered to detect changes in blood pressure.

[0341] Additionally, methods of treating hypertension by administering siRNAs which target human AGT have been proposed, including, e.g., zilebesiran (also referred to as ALN-AGT01), see, e.g., WO2019/222166; Ranasinghe et al. (2022) *J Am Heart Assoc.* 11(20); e027694 (Ranasinghe et al. (2022)). It has been postulated that essentially complete depletion of AGT by siRNA therapy could prevent RAAS escape (such as occurs with a compensatory increase in renin levels due to decreased blood pressure and loss of negative feedback mediated by Ang II when standard RAAS inhibitors, e.g., ACEi and ARB, are used), yielding more effective RAAS inhibition and long-term blood pressure control (see, e.g., Ren et al. (2020) *Curr Opin Nephrol Hypertens* 29(2):180-189). It has

also been suggested that a major advantage of RNAi-based therapeutic applications over antisense oligonucleotide (ASO)-based therapies is a purported relatively more potent and longer inhibitory effect of RNAi-based therapeutics (see, e.g., Ren et al. (2020) *Curr Opin Nephrol Hypertens* 29(2):180-189). A report of a phase 1 study of zilebesiran involving subjects with hypertension describes decreases in serum AGT levels and blood pressure after single subcutaneous doses (up to 800 mg) of the compound were sustained for up to 4 weeks (See Desai et al. (2023) *N Eng J Med* 389(3):228-238 (Desai et al. (2023))). Mean decreases in AGT levels of more than 90% (zilebesiran doses of 100 mg or more) sustained from week 3 through week 12, or through week 24 (800 mg zilebesiran) were observed. Hypotension, hyperkalemia, or worsening of renal function resulting in medical intervention was not reported; however, the study was not large enough or of sufficient duration to assess uncommon serious events (enrollment was restricted to younger persons with stage 1-2 hypertension who did not have serious co-existing medical conditions). Blood pressure changes after zilebesiran treatment could be reversed through high dietary salt intake and were augmented by coadministration of an ARB (irbesartan). It has been noted that recovery of zilebesiran-associated decreases in blood pressure after exposure to high dietary salt intake suggests that development of hypotension during zilebesiran treatment could be partially reversed by raising salt intake as an adjunct to standard interventions, including volume resuscitation and pressor support (Desai et al. (2023)). Ranasinghe et al. (2022) also note that results suggest that oral sodium (or if severe, intravenous, alongside vasopressors) could be used clinically where hypotension and hypovolemia must be reversed. Based on the potential for clinical need to reverse effects of AGT-targeting siRNA, strategies to overcome the blood pressure-lowering effects of these agents have been examined in spontaneously hypertensive rats: AGT-targeting siRNA caused a near complete depletion of AGT (by $99.2 \pm 0.1\%$) and a reduction in mean arterial pressure by 19mm Hg, similar to results observed with zilebesiran (800 mg) in the phase 1 trial; and effects could be reversed by continuous infusion of intravenous vasopressors (Ang II or norepinephrine) ((Uijl et al. (2022) *J Am Heart Assoc* 11(15); e026426); Ranasinghe et al. (2022))).

[0342] Additional antisense oligonucleotides, including compound 1205407, have been described previously wherein compound 1205407 (also known as ION904) was identified to be more potent than earlier identified compounds. (see WO2022/109139). As described herein, studies of ION904 in healthy subject and in subjects with uncontrolled hypertension maintaining their existing antihypertension medication regimen demonstrated that it is well tolerated with no drug related

SAEs, no AE signals, no clinically meaningful changes in laboratory assessments, no hypotensive events, no acute renal changes or changes in renal function, no clinically relevant hyperkalemia, and no thrombocytopenia; and while reduction in plasma AGT protein level was significantly greater than reported for compound 757456, and achieved up to 86% reduction as compared to baseline, insignificant reduction in systolic blood pressure was observed in the treatment groups compared to placebo. (see Examples 3 and 4). Without being bound by theory, it is believed compositions and methods provided herein sufficiently reduce the amount or level of AGT RNA and/or AGT protein in a subject having or at risk for heart failure to provide a therapeutic benefit but with limited effect on blood pressure (and other cardiovascular/renal parameters affected by the RAAS), thereby markedly reducing risk of adverse events or side effects associated with other RAAS inhibitors.

[0343] Thus, provided herein, are compositions and methods for reducing AGT RNA and/or AGT protein in a subject having or at risk for heart failure and for treating, or ameliorating at least one symptom of heart failure in, a subject having or at risk for heart failure. In certain embodiments, the heart failure is HFrEF. In certain embodiments, compositions and methods are provided for reducing AGT RNA and/or AGT protein in a subject having or at risk for heart failure (e.g., HFrEF) and for treating a subject having or at risk for heart failure (e.g., HFrEF) wherein the subject is, or is at risk of being, susceptible to adverse side effects of existing RAAS inhibitor therapies, including, but not limited to, ACE inhibitors (ACEi), ARBs, ARNi, and MRAs. In certain embodiments, a subject is unable to tolerate treatment with optimal, Guideline-recommended target doses or dosing regimens of RAAS inhibitors (e.g., ACEi, ARB, ARNi, MRA) for treatment of heart failure. In certain embodiments, a subject has hyperkalemia, renal dysfunction, renal insufficiency (including AKI and CKD), hypotension, and/or pulmonary disease. In certain embodiments, a subject has or is at risk of having angioedema, asthma or chronic obstructive pulmonary disease (COPD). In certain embodiments, compositions provided herein, and methods for reducing AGT RNA and/or AGT protein or for treating a subject having or at risk for heart failure, provide for at least a 70%, at least a 75%, at least an 80%, or at least an 85% decrease in the amount or level of AGT RNA and/or AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT plasma protein of the subject, or circulating level of AGT protein) compared to the level of AGT RNA and/or AGT protein prior to any treatment with the compositions and methods (i.e., baseline AGT RNA or AGT protein levels) wherein the maximum decrease in the amount of AGT RNA and/or AGT protein is less than 95%, or less 94%, or less than 93%, or less than 92%, or less than 91%, or less than of 90%, or less than

88%, or less than 86%, or less than 85%, compared to the amount or level of AGT RNA and/or AGT protein prior to any treatment with the compositions and methods (i.e., baseline level). In certain embodiments of the compositions and methods, the composition contains or consists essentially of, or the method for reducing AGT RNA and/or AGT protein, or for treating a subject having or at risk for heart failure (e.g., HFrEF) includes administration of, a single-stranded oligomeric agent (such as, for example, a single-stranded modified oligonucleotide, e.g., a single-stranded modified antisense oligonucleotide) having a nucleobase sequence complementary to a target region sequence in an AGT nucleic acid. In certain embodiments, the oligomeric agent is ION904. In certain embodiments, the amount of ION904 is within the range of about 60 mg to about 120 mg, about 75 mg to about 120 mg, about 80 mg to about 120 mg, or about 90 to about 100 mg. In certain embodiments, ION904 is administered once every 4 weeks or once a month. In certain embodiments, ION904 or a composition containing ION904 is administered for a period of about 1 month to about 12 months, or about 6 months to about 36 months, or about 12 months to about 60 months or more.

[0344] B. Oligomeric Agents

[0345] In certain embodiments of compositions and methods described herein, a composition contains, or a method includes administering to a cell or subject, an oligomeric agent comprising or consisting of at least one modified oligonucleotide and optionally one or more additional associated features selected from: (a) one or more additional oligonucleotides, each of which may be modified or unmodified, hybridized to or covalently linked to the at least one modified oligonucleotide and/or to each other; (b) one or more conjugate groups, which may be covalently attached directly or indirectly to an oligonucleotide of such oligomeric agent; and (c) one or more terminal groups. In certain embodiments, an oligomeric agent comprises or consists of a modified oligonucleotide comprising a nucleobase sequence that is complementary to an equal length target region of a target nucleic acid, such as an AGT target nucleic acid (e.g., a human AGT target nucleic acid). In certain embodiments, the AGT nucleic acid has the sequence set forth in SEQ ID NO: 1 or SEQ ID NO: 2.

[0346] In certain embodiments, an oligomeric agent contains or consists of a modified oligonucleotide, such as, for example, an antisense oligonucleotide, containing a nucleobase sequence complementary to an AGT RNA, e.g., a human AGT RNA, such as a mature AGT mRNA or an AGT pre-mRNA, including intronic, exonic, and untranslated regions. In certain embodiments, the modified oligonucleotide, is single-stranded. In certain embodiments, the

modified oligonucleotide, is double-stranded. In certain embodiments, contacting a cell with an oligomeric agent containing a modified oligonucleotide, containing a nucleobase sequence that is complementary to an equal-length target region of SEQ ID NOs: 1 or 2 decreases the amount or level of AGT RNA in the cell, and in certain embodiments decreases the amount or level of AGT protein produced in the cell. In certain embodiments, the oligonucleotide is attached to a conjugate group, e.g., a conjugate group containing a cell-targeting moiety that interacts with or binds to a cell surface protein of a hepatic cell. In certain embodiments, the oligonucleotide is attached to a conjugate group containing one or more N-acetyl galactosamine (GalNAc) moieties. In certain embodiments, the oligomeric agent consists of an oligonucleotide attached to a conjugate group, e.g., a conjugate group containing one or more GalNAc moieties. In certain embodiments, the conjugate group is attached to a terminus of the oligonucleotide, e.g., the 5' terminal nucleobase of the oligonucleotide. In certain embodiments, a modified oligonucleotide of the oligomeric agent is an antisense oligonucleotide. In certain embodiments, the oligomeric agent comprises or consists of an antisense oligonucleotide. In certain embodiments, the oligomeric agent comprises or consists of an antisense oligonucleotide and a conjugate group. In certain embodiments, the oligomeric agent consists of an antisense oligonucleotide attached to a conjugate group, e.g., a conjugate group containing one or more GalNAc moieties. In certain embodiments, the oligomeric agent comprises or consists of an antisense oligonucleotide and one or more terminal group(s). In certain embodiments, the oligomeric agent comprises or consists of an antisense oligonucleotide, a conjugate group, and one or more terminal group(s). In certain embodiments, the oligomeric agent comprises or consists of an antisense oligonucleotide comprising a nucleobase sequence that is complementary to a target region of an AGT nucleic acid, and a sense oligonucleotide comprising a duplexing region that is complementary to the antisense oligonucleotide, or a region thereof. In certain embodiments, one or both of the antisense and sense oligonucleotides is/are modified. In certain embodiments, the antisense oligonucleotide and/or the sense oligonucleotide is attached to a conjugate group and/or a terminal group. Modified antisense and/or sense oligonucleotides comprise at least one modified nucleoside (comprising a modified sugar moiety and/or a modified nucleobase and/or lacking a nucleobase) and/or at least one modified internucleoside linkage. Examples of certain modified nucleosides and modified internucleoside linkages suitable for use in modified antisense and/or sense oligonucleotides are described herein. In certain embodiments, an oligomeric agent is an RNase H agent. In certain embodiments, an oligomeric agent is an RNAi agent.

[0347] In certain embodiments, the oligomeric agent containing a modified oligonucleotide (such as, for example, a single-stranded modified oligonucleotide), containing a nucleobase sequence complementary to an equal length target region of an AGT target nucleic acid (e.g., a human AGT target nucleic acid, such as, for example, the AGT nucleic acid having the sequence set forth in SEQ ID NO: 1 or SEQ ID NO: 2), when administered to a cell or subject, decreases the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 70%, at least 75%, at least 80%, or at least 85% and less than 95% compared to the amount or level of AGT RNA and/or AGT protein prior to any administration of the oligomeric agent (i.e., the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject). In certain embodiments, the maximum decrease in the amount or level of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT protein) is less than 95%, or less than 94%, or less than 93%, or less than 92%, or less than 91%, or less than 90% compared to the amount or level of AGT RNA and/or AGT protein prior to any administration of the oligomeric agent. In certain embodiments, the amount or level of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT protein) decreases no more than 85%, or no more than 86%, or no more than 87%, or no more than 88%, or no more than 89%, or no more than 90%, or no more than 91%, or no more than 92%, or no more than 93%, or no more than 94% compared to the amount or level of AGT RNA and/or AGT protein prior to any administration of the oligomeric agent. In certain embodiments, the oligomeric agent, when administered to a cell or subject, decreases the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared to the amount or level of AGT RNA and/or AGT protein prior to any administration of the oligomeric agent (i.e., the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject). In certain embodiments, the oligomeric agent, when administered to a cell or subject, decreases the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 70%, at least 75%, at least 80% or at least 85% and less than 94% compared to the amount or level of AGT RNA and/or AGT protein

prior to any administration of the oligomeric agent (i.e., the baseline level or amount of AGT RNA and/or AGT protein in a cell or subject). In certain embodiments, the oligomeric agent, when administered to a cell or subject, decreases the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 70%, at least 75%, at least 80% or at least 85% and less than 93% compared to the amount or level of AGT RNA and/or AGT protein prior to any administration of the oligomeric agent (i.e., the baseline level or amount of AGT RNA and/or AGT protein in a cell or subject). In certain embodiments, the oligomeric agent, when administered to a cell or subject, decreases the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 70%, at least 75%, at least 80% or at least 85% and less than 92% compared to the amount or level of AGT RNA and/or AGT protein prior to any administration of the oligomeric agent (i.e., the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject). In certain embodiments, the oligomeric agent, when administered to a cell or subject, decreases the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 70%, at least 75%, at least 80% or at least 85% and less than 91% compared to the amount or level of AGT RNA and/or AGT protein prior to any administration of the oligomeric agent (i.e., the baseline level or amount of AGT RNA and/or AGT protein in a cell or subject). In certain embodiments, the oligomeric agent, when administered to a cell or subject, decreases the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 70%, at least 75%, at least 80% or at least 85% and less than 90% compared to the amount or level of AGT RNA and/or AGT protein prior to any administration of the oligomeric agent (i.e., the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject). In certain embodiments, the oligomeric agent, when administered to a cell or subject, decreases the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 70%, at least 75%, at least 80% or at least 85% and less than 89% compared to the amount or level of AGT RNA and/or AGT protein prior to any administration of the oligomeric agent (i.e., the baseline level or amount of AGT RNA

and/or AGT protein in the cell or subject). In certain embodiments, the oligomeric agent, when administered to a cell or subject, decreases the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 70% but less than 95%, less than 94%, less than 93%, less than 92%, less than 91%, less than 90%, less than 89%, less than 88%, less than 87%, less than 86%, or less than 85% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, the oligomeric agent, when administered to a cell or subject, decreases the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 75% but less than 95%, less than 94%, less than 93%, less than 92%, less than 91%, less than 90%, less than 89%, less than 88%, less than 87%, less than 86%, or less than 85% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, the oligomeric agent, when administered to a cell or subject, decreases the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 80% but 95%, less than 94%, less than 93%, less than 92%, less than 91%, less than 90%, less than 89%, less than 88%, less than 87%, less than 86%, or less than 85% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, the oligomeric agent, when administered to a cell or subject, decreases the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 85% but less than 95%, less than 94%, less than 93%, less than 92%, less than 91%, less than 90%, or less than 89% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, the oligomeric agent, when administered to a cell or subject, decreases the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by 70%-90%, 70%-89%, 70%-88%, 70%-87%, 70%-86%, 70%-85%, 70%-84%, 70%-83%, 70%-82%, 70%-81%, 70%-80%, 75%-90%, 75%-89%, 75%-88%, 75%-87%, 75%-86%, 75%-85%, 75%-84%, 75%-83%, 75%-82%, 75%-81%, 75%-80%, 76%-90%, 76%-89%, 76%-88%, 76%-87%, 76%-86%, 76%-85%, 76%-84%, 76%-83%, 76%-82%, 76%-81%, 76%-80%, 77%-90%, 77%-89%, 77%-88%, 77%-87%, 77%-86%,

77%-85%, 77%-84%, 77%-83%, 77%-82%, 77%-81%, 77%-80%, 78%-90%, 78%-89%, 78%-88%, 78%-87%, 78%-86%, 78%-85%, 78%-84%, 78%-83%, 78%-82%, 78%-81%, 78%-80%, 79%-90%, 79%-89%, 79%-88%, 79%-87%, 79%-86%, 79%-85%, 79%-84%, 79%-83%, 79%-82%, 79%-81%, 79%-80%, 80%-90%, 80%-89%, 80%-88%, 80%-87%, 80%-86%, 80%-85%, 80%-84%, 80%-83%, 80%-82%, 81%-90%, 81%-89%, 81%-88%, 81%-87%, 81%-86%, 81%-85%, 81%-84%, 81%-83%, 81%-82%, 82%-90%, 82%-89%, 82%-88%, 82%-87%, 82%-86%, 82%-85%, 82%-84%, 82%-83%, 83%-90%, 83%-89%, 83%-88%, 83%-87%, 83%-86%, 83%-85%, 83%-84%, 84%-90%, 84%-89%, 84%-88%, 84%-87%, 84%-86%, 84%-85%, 85%-90%, 85%-89%, 85%-88%, 85%-87%, 85%-86%, 86%-90%, 86%-89%, 86%-88%, 86%-87%, 87%-90%, 87%-89%, 87%-88%, 88%-90%, or 88%-89% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject.

[0348] In certain embodiments of compositions and methods described herein, a composition contains, or a method includes administering to a cell or subject, an oligomeric agent comprising or consisting of a modified oligonucleotide, containing a nucleobase sequence at least 80% complementary to an equal length region of nucleobases 2046-2061 of SEQ ID NO: 1 or nucleobases 14940-14955 of SEQ ID NO: 2. In certain embodiments, the oligomeric agent contains a conjugate group. In certain embodiments, the oligomeric agent consists of a modified oligonucleotide, containing a nucleobase sequence at least 80% complementary to an equal length region of nucleobases 2046-2061 of SEQ ID NO: 1 or nucleobases 14940-14955 of SEQ ID NO: 2 attached to a conjugate group. In certain embodiments, the conjugate group contains a cell-targeting moiety that interacts with or binds to a cell surface protein of a hepatic cell. In certain embodiments, the oligonucleotide is attached to a conjugate group containing one or more GalNAc moieties. In certain embodiments, the conjugate group is attached to a terminus of the oligonucleotide, e.g., the 5' terminal nucleobase of the oligonucleotide.

[0349] In certain embodiments of compositions and methods described herein, a composition contains, or a method includes administering to a cell or subject, an oligomeric agent comprising or consisting of a modified oligonucleotide, having a nucleobase sequence of SEQ ID NO: 3. In certain embodiments, the oligomeric agent contains a conjugate group. In certain embodiments, the oligomeric agent consists of a modified oligonucleotide, having a nucleobase sequence of SEQ ID NOs: 3, 4 or 5 attached to a conjugate group. In certain embodiments, the conjugate group contains a cell-targeting moiety that interacts with or binds to a cell surface protein of a hepatic cell. In

certain embodiments, the oligonucleotide is attached to a conjugate group containing one or more GalNAc moieties. In certain embodiments, the conjugate group is attached to a terminus of the oligonucleotide, e.g., the 5' terminal nucleobase of the oligonucleotide.

[0350] In certain embodiments of compositions and methods described herein, a composition contains or consists of, or a method includes administering to a cell or subject, a compound comprising or consisting of a modified oligonucleotide according to the following chemical notation (5' to 3'):

${}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 4); wherein,

A = an adenine nucleobase,

${}^m\text{C}$ = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

k = a cEt sugar moiety,

d = an unmodified DNA sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

[0351] In certain embodiments of compositions and methods described herein, a composition contains or consists of, or a method includes administering to a cell or subject, ION904. In certain embodiments, ION904 is represented by the following chemical notation (5' to 3'):

[0352] $\text{THA-C6-GalNAc}_3\text{-}{}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 5); wherein,

A = an adenine nucleobase,

${}^m\text{C}$ = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

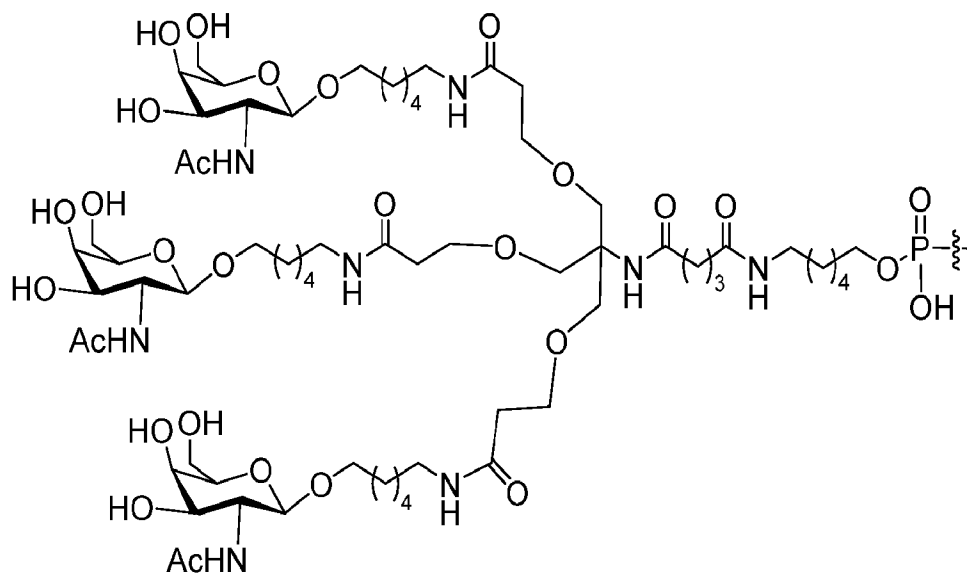
k = a cEt sugar moiety,

d = an unmodified DNA sugar moiety,

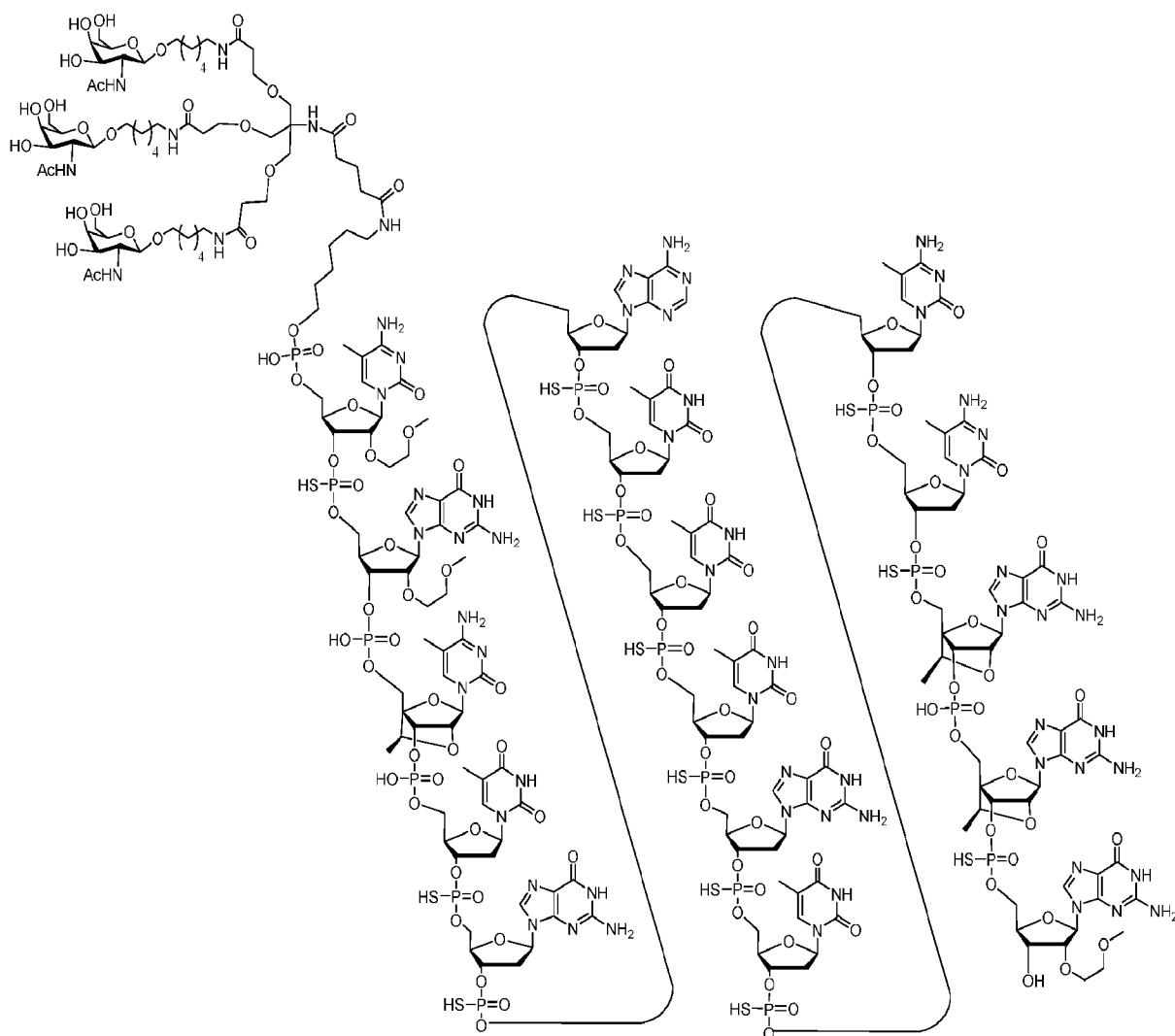
s = a phosphorothioate internucleoside linkage,

o = a phosphodiester internucleoside linkage, and

THA-C6-GalNAc₃=



[0353] In certain embodiments, ION904 is represented by the following chemical structure:



(SEQ ID NO: 5 having the nucleobase sequence of SEQ ID NO: 3) (Structure 1),

or a salt thereof.

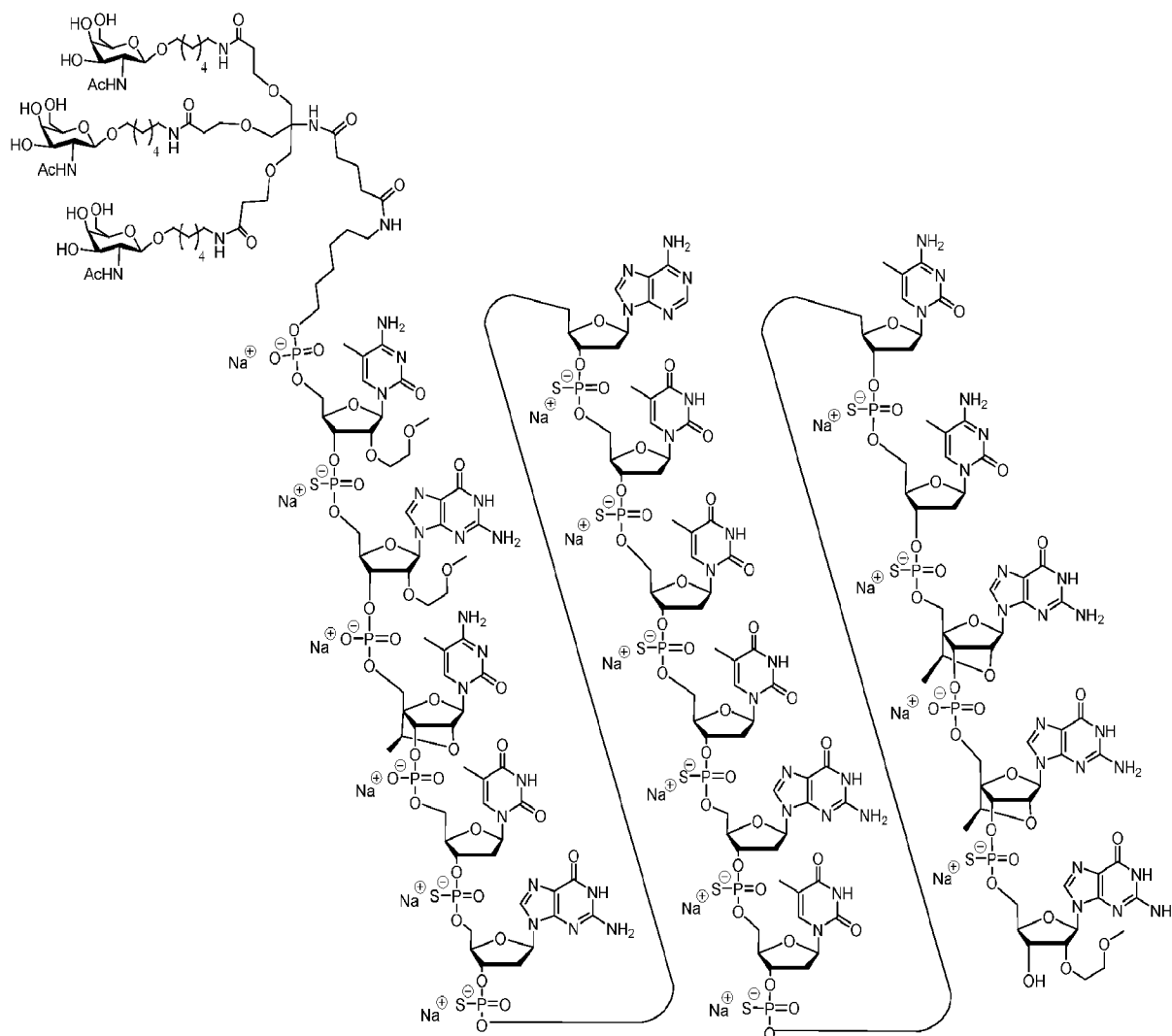
[0354] Under certain conditions, an oligomeric agent, e.g., ION904, acts as an acid. For example, although an oligomeric agent such as ION904 may be drawn or described in protonated (free acid) form, or ionized and in association with a cation (salt) form, aqueous solutions of the oligomeric agent, e.g., ION904, exist in equilibrium among such forms. For example, a phosphate linkage of ION904 in aqueous solution exists in equilibrium among free acid, anion, and salt forms. Unless otherwise indicated, the term, “ION904,” is intended to include all such forms. Moreover, ION904 has several such linkages, each of which is in equilibrium. Thus, ION904 exists in solution in an ensemble of forms at multiple positions all at equilibrium. The term “ION904” 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 ION904 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.

[0355] In certain embodiments, ION904 is in aqueous solution with sodium. In certain embodiments, ION904 is in aqueous solution with potassium. In certain embodiments, ION904 is in phosphate-buffered saline (PBS). In certain embodiments, ION904 is in water. In certain embodiments, the pH of the solution is adjusted with NaOH and/or HCl to achieve a desired pH.

[0356] In certain embodiments, ION904 is a pharmaceutically acceptable salt comprising one or more cations selected from sodium, potassium, calcium, and magnesium. In certain embodiments, ION904 is a sodium salt or a potassium salt.

[0357] In certain embodiments, the fully sodiated sodium salt of ION904 is represented by the following chemical structure:



(SEQ ID NO: 5 having the nucleobase sequence of SEQ ID NO: 3) (Structure 2).

[0358] C. Oligonucleotides

[0359] In certain embodiments, modified oligonucleotides useful in the methods and compositions described herein are described by their nucleobase sequence. In certain embodiments, oligonucleotides have a nucleobase sequence that is complementary to a nucleobase sequence of a second strand of linked nucleosides (*e.g.*, another oligonucleotide or an identified reference nucleic acid, such as a target nucleic acid) or a region thereof. In certain embodiments, a region of an oligonucleotide has a nucleobase sequence that is complementary to a nucleobase sequence of a second strand of linked nucleosides or a region thereof. In certain embodiments, the nucleobase sequence of a region or entire length of an oligonucleotide is at least 70%, at least 80%, at least 85%, at least 90%, at least 95%, or 100% complementary to the nucleobase sequence of a second strand of linked nucleosides or region thereof.

[0360] In certain embodiments of compositions and methods described herein, a composition contains, or a method includes administering, an oligomeric agent comprising or consisting of a modified oligonucleotide, containing a nucleobase sequence that is complementary to an equal length nucleobase sequence of a target nucleic acid. In certain embodiments, the target nucleic acid is an AGT target nucleic acid (*e.g.*, a human AGT target nucleic acid). In certain embodiments, the AGT nucleic acid has the sequence set forth in SEQ ID NO: 1 or SEQ ID NO: 2.

[0361] In certain embodiments, a modified oligonucleotide, comprises or consists of a nucleobase sequence that is at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% complementary to a region of SEQ ID NOs: 1 or 2. In certain embodiments, a modified oligonucleotide, comprises or consists of a nucleobase sequence that is at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% complementary to an equal length nucleobase sequence of nucleobases 2046-2061 of SEQ ID NO: 1 or nucleobases 14940-14955 of SEQ ID NO: 2. In certain embodiments, a modified oligonucleotide comprises or consists of a nucleobase sequence that is 100% complementary to a nucleobase sequence of SEQ ID NOs: 1 or 2. In certain embodiments, a modified oligonucleotide comprises or consists of a nucleobase sequence that is 100% complementary to an equal length sequence of nucleobases 2046-2061 of SEQ ID NO: 1 or nucleobases 14940-14955 of SEQ ID NO: 2. In certain embodiments, a modified oligonucleotide, has a nucleobase sequence comprising or consisting of any of SEQ ID NOs: 3, 4 or 5, with 0, 1 or 2 mismatches. In certain embodiments, a modified oligonucleotide, has a nucleobase sequence comprising or consisting of any of SEQ ID NOs: 3, 4 or 5.

[0362] In certain embodiments, the oligonucleotide (e.g., modified oligonucleotide) is complementary to a target region of an AGT nucleic acid over the entire length of the oligonucleotide. In certain embodiments, a modified oligonucleotide is at least 99%, at least 95%, at least 90%, at least 85%, or at least 80% complementary to an equal length portion of the AGT nucleic acid. In certain embodiments, the modified oligonucleotide is at least 80% complementary to a region of the AGT nucleic acid over the entire length of the oligonucleotide and comprises a nucleobase sequence that is 100% or fully complementary to a target region of the AGT nucleic acid.

[0363] In certain embodiments, a targeting region nucleobase sequence of a modified oligonucleotide is from 6 to 20, 10 to 18, 14 to 18, 15 to 16, 16 to 17, 16 to 20, or 18 to 20 nucleosides in length. In certain embodiments, the targeting region nucleobase sequence comprises at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, or at least 23 contiguous nucleosides. In certain embodiments, the targeting region nucleobase sequence is 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23 contiguous nucleosides in length. In certain embodiments, the targeting region nucleobase sequence constitutes at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% of the nucleosides of the oligonucleotide. In certain embodiments, the targeting region nucleobase sequence constitutes all of the nucleosides of the oligonucleotide. In certain embodiments, the targeting region nucleobase sequence of the oligonucleotide is at least 99%, at least 95%, at least 90%, at least 85%, or at least 80% complementary to the AGT nucleic acid. In certain embodiments, the targeting region nucleobase sequence of the oligonucleotide is 100% complementary to a nucleobase sequence of the AGT nucleic acid.

[0364] It is possible to increase or decrease the length of an oligonucleotide without eliminating activity. For example, in Woolf *et al. Proc. Natl. Acad. Sci. USA* 1992, 89:7305-7309, a series of oligonucleotides 13-25 nucleosides in length were tested for their ability to induce cleavage of a target RNA in an oocyte injection model. Oligonucleotides 25 nucleosides in length with 8 or 11 mismatch bases near the ends of the oligonucleotides were able to direct specific cleavage of the target RNA, albeit to a lesser extent than the oligonucleotides that contained no mismatches. Similarly, target specific cleavage was achieved using 13 nucleobase oligonucleotides, including those with 1 or 3 mismatches.

[0365] In certain embodiments, an oligonucleotide (including modified oligonucleotides, antisense oligonucleotides, oligonucleotides contained in oligomeric agents) has any of a variety of ranges of lengths. In certain embodiments, oligonucleotides consist of X to Y linked nucleosides, where X represents the fewest number of nucleosides in the range and Y represents the largest number nucleosides in the range. In certain embodiments, X and Y are each independently selected from 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, and 50; provided that $X \leq Y$. For example, in certain embodiments, oligonucleotides consist of 12 to 13, 12 to 14, 12 to 15, 12 to 16, 12 to 17, 12 to 18, 12 to 19, 12 to 20, 12 to 21, 12 to 22, 12 to 23, 12 to 24, 12 to 25, 12 to 26, 12 to 27, 12 to 28, 12 to 29, 12 to 30, 13 to 14, 13 to 15, 13 to 16, 13 to 17, 13 to 18, 13 to 19, 13 to 20, 13 to 21, 13 to 22, 13 to 23, 13 to 24, 13 to 25, 13 to 26, 13 to 27, 13 to 28, 13 to 29, 13 to 30, 14 to 15, 14 to 16, 14 to 17, 14 to 18, 14 to 19, 14 to 20, 14 to 21, 14 to 22, 14 to 23, 14 to 24, 14 to 25, 14 to 26, 14 to 27, 14 to 28, 14 to 29, 14 to 30, 15 to 16, 15 to 17, 15 to 18, 15 to 19, 15 to 20, 15 to 21, 15 to 22, 15 to 23, 15 to 24, 15 to 25, 15 to 26, 15 to 27, 15 to 28, 15 to 29, 15 to 30, 16 to 17, 16 to 18, 16 to 19, 16 to 20, 16 to 21, 16 to 22, 16 to 23, 16 to 24, 16 to 25, 16 to 26, 16 to 27, 16 to 28, 16 to 29, 16 to 30, 17 to 18, 17 to 19, 17 to 20, 17 to 21, 17 to 22, 17 to 23, 17 to 24, 17 to 25, 17 to 26, 17 to 27, 17 to 28, 17 to 29, 17 to 30, 18 to 19, 18 to 20, 18 to 21, 18 to 22, 18 to 23, 18 to 24, 18 to 25, 18 to 26, 18 to 27, 18 to 28, 18 to 29, 18 to 30, 19 to 20, 19 to 21, 19 to 22, 19 to 23, 19 to 24, 19 to 25, 19 to 26, 19 to 27, 19 to 28, 19 to 29, 19 to 30, 20 to 21, 20 to 22, 20 to 23, 20 to 24, 20 to 25, 20 to 26, 20 to 27, 20 to 28, 20 to 29, 20 to 30, 21 to 22, 21 to 23, 21 to 24, 21 to 25, 21 to 26, 21 to 27, 21 to 28, 21 to 29, 21 to 30, 22 to 23, 22 to 24, 22 to 25, 22 to 26, 22 to 27, 22 to 28, 22 to 29, 22 to 30, 23 to 24, 23 to 25, 23 to 26, 23 to 27, 23 to 28, 23 to 29, 23 to 30, 24 to 25, 24 to 26, 24 to 27, 24 to 28, 24 to 29, 24 to 30, 25 to 26, 25 to 27, 25 to 28, 25 to 29, 25 to 30, 26 to 27, 26 to 28, 26 to 29, 26 to 30, 27 to 28, 27 to 29, 27 to 30, 28 to 29, 28 to 30, or 29 to 30 linked nucleosides.

[0366] In certain embodiments, modified oligonucleotides consist of 16 linked nucleosides. In certain embodiments, oligonucleotides modified oligonucleotides consist of 14 linked nucleosides. In certain embodiments, modified oligonucleotides consist of 15 linked nucleosides. In certain embodiments, modified oligonucleotides consist of 17 linked nucleosides. In certain embodiments, modified oligonucleotides consist of 18 linked nucleosides. In certain embodiments, modified oligonucleotides consist of 19 linked nucleosides. In certain embodiments, modified oligonucleotides consist of 20 linked nucleosides. In certain embodiments, modified

oligonucleotides consist of 21 linked nucleosides. In certain embodiments, modified oligonucleotides consist of 22 linked nucleosides. In certain embodiments, modified oligonucleotides consist of 23 linked nucleosides. In certain embodiments, modified oligonucleotides have no more than 1 to 3 mismatches to a target nucleic acid.

[0367] In certain embodiments, modified oligonucleotides consist of 12-30 linked nucleosides. In certain embodiments, modified oligonucleotides consist of 14-25 linked nucleosides. In certain embodiments, modified oligonucleotides consist of 14-23 linked nucleosides. In certain embodiments, modified oligonucleotides consist of 14-20 linked nucleosides. In certain embodiments, modified oligonucleotides consist of 14-18 linked nucleosides. In certain embodiments, modified oligonucleotides consist of 14-17 linked nucleosides. In certain embodiments, modified oligonucleotides consist of 14-16 linked nucleosides. In certain embodiments, modified oligonucleotides consist of 16-23 linked nucleosides. In certain embodiments, modified oligonucleotides consist of 16-20 linked nucleosides. In certain embodiments, modified oligonucleotides consist of 16-30 linked nucleosides. In certain embodiments, modified oligonucleotides consist of 19-30 linked nucleosides. In certain embodiments, modified oligonucleotides consist of 23-30 linked nucleosides. In certain embodiments, modified oligonucleotides consist of 18-25 linked nucleosides. In certain embodiments, modified oligonucleotides consist of 16-22 linked nucleosides. In certain embodiments, modified oligonucleotides consist of 18-19 linked nucleosides. In certain embodiments, modified oligonucleotides consist of 21-23 linked nucleosides. In certain embodiments, modified oligonucleotides consist of 23-24 linked nucleosides. In certain embodiments, modified oligonucleotides consist of 16 linked nucleosides. In certain embodiments, modified oligonucleotides consist of 17 linked nucleosides. In certain embodiments, modified oligonucleotides consist of 18 linked nucleosides. In certain embodiments, modified oligonucleotides consist of 19 linked nucleosides. In certain embodiments, modified oligonucleotides consist of 20 linked nucleosides. In certain embodiments, modified oligonucleotides consist of 21 linked nucleosides. In certain embodiments, modified oligonucleotides consist of 22 linked nucleosides. In certain embodiments, modified oligonucleotides consist of 23 linked nucleosides.

[0368] In certain embodiments, a modified oligonucleotide contains one or more mismatches relative to the nucleobase sequence of the target AGT nucleic acid. In certain embodiments, the

oligonucleotide is an antisense oligonucleotide. In certain embodiments, antisense activity against the target nucleic acid is reduced by such a mismatch, and activity against a non-target nucleic acid is reduced. In certain embodiments, activity against the non-target nucleic acid is reduced by a greater amount than activity against the target nucleic acid. Thus, in certain embodiments selectivity of the antisense oligonucleotide is improved. In certain embodiments, the oligonucleotide, e.g., antisense oligonucleotide, is at least 80% complementary to the target region of the AGT nucleic acid over the entire length of the oligonucleotide and comprises no more than one to three mismatches with the AGT nucleic acid. In certain embodiments, the oligonucleotide comprises a nucleobase sequence that is at least 80% complementary to a nucleobase sequence of the AGT nucleic acid over the entire length, and comprises no more than one to three mismatches with the target nucleic acid. In certain embodiments, the oligonucleotide, e.g., an antisense oligonucleotide, comprises a nucleobase sequence that is at least 80%, at least 85%, at least 90%, at least 95%, or 100% complementary to a the AGT nucleic acid over the entire length of the nucleobase sequence. In certain embodiments, a mismatch is specifically positioned within an oligonucleotide, e.g., an antisense oligonucleotide. In certain embodiments, a mismatch is at position 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 from the 5'-end of the oligonucleotide. In certain embodiments, a mismatch is at position 11, 10, 9, 8, 7, 6, 5, 4, 3, or 2 from the 3'-end of the oligonucleotide. In certain embodiments, 1-2 additional mismatches may be present at a terminus or at both termini of the oligonucleotide. In certain embodiments, a mismatch is at position 1, 2, 3, or 4 from the 5'-end of the oligonucleotide. In certain embodiments, a mismatch is at position 4, 3, 2, or 1 from the 3'-end of the oligonucleotide.

[0369] In certain embodiments, a modified oligonucleotide (such as, for example, a single-stranded modified oligonucleotide), containing a nucleobase sequence complementary to an equal length target region of an AGT target nucleic acid (e.g., a human AGT target nucleic acid, such as, for example, the AGT nucleic acid having the sequence set forth in SEQ ID NO: 1 or SEQ ID NO: 2), when administered to a cell or subject, decreases the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 70%, at least 75%, at least 80%, or at least 85% compared to the amount or level of AGT RNA and/or AGT protein prior to any administration of the oligomeric agent (i.e., the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject). In certain embodiments, the maximum decrease in the amount or level

of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT protein) is less than less than 95%, or less than 94%, or less than 93%, or less than 92%, or less than 91%, or less than 90% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, the amount or level of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT protein) decreases no more than 85%, or no more than 86%, or no more than 87%, or no more than 88%, or no more than 89%, or no more than 90%, or no more than 91%, or no more than 92%, or no more than 93%, or no more than 94%, or no more than 95%, compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, the oligonucleotide, e.g., modified oligonucleotide (such as, for example, a single-stranded modified oligonucleotide), when administered to a cell or subject, decreases the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, the oligonucleotide, when administered to a cell or subject, decreases the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 70%, at least 75%, at least 80% or at least 85% and less than 94% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, the oligonucleotide, e.g., modified oligonucleotide (such as, for example, a single-stranded modified oligonucleotide), when administered to a cell or subject, decreases the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 70%, at least 75%, at least 80% or at least 85% and less than 93% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, the oligonucleotide, e.g., modified oligonucleotide (such as, for example, a single-stranded modified oligonucleotide), when administered to a cell or subject, decreases the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 70%, at least 75%, at least 80% or at

least 85% and less than 92% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, the oligonucleotide, e.g., modified oligonucleotide (such as, for example, a single-stranded modified oligonucleotide), when administered to a cell or subject, decreases the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 70%, at least 75%, at least 80% or at least 85% and less than 91% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, the oligonucleotide, e.g., modified oligonucleotide (such as, for example, a single-stranded modified oligonucleotide), when administered to a cell or subject, decreases the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 70%, at least 75%, at least 80% or at least 85% and less than 90% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, the oligonucleotide, e.g., modified oligonucleotide (such as, for example, a single-stranded modified oligonucleotide), when administered to a cell or subject, decreases the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 70%, at least 75%, at least 80% or at least 85% and less than 89% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, the oligonucleotide, e.g., modified oligonucleotide (such as, for example, a single-stranded modified oligonucleotide), when administered to a cell or subject, decreases the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 70% but less than 95%, less than 94%, less than 93%, less than 92%, less than 91%, less than 90%, less than 89%, less than 88%, less than 87%, less than 86%, or less than 85% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, the oligonucleotide, e.g., modified oligonucleotide (such as, for example, a single-stranded modified oligonucleotide), when administered to a cell or subject, decreases the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 75% but less than 95%, less than

94%, less than 93%, less than 92%, less than 91%, less than 90%, less than 89%, less than 88%, less than 87%, less than 86%, or less than 85% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, the oligonucleotide, e.g., modified oligonucleotide (such as, for example, a single-stranded modified oligonucleotide), when administered to a cell or subject, decreases the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 80% but less than 95%, less than 94%, less than 93%, less than 92%, less than 91%, less than 90%, less than 89%, less than 88%, less than 87%, less than 86%, or less than 85% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, the oligonucleotide, e.g., modified oligonucleotide (such as, for example, a single-stranded modified oligonucleotide), when administered to a cell or subject, decreases the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 85% but less than 95%, less than 94%, less than 93%, less than 92%, less than 91%, less than 90%, or less than 89% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, the oligonucleotide, e.g., modified oligonucleotide (such as, for example, a single-stranded modified oligonucleotide), when administered to a cell or subject, decreases the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by 70%-90%, 70%-89%, 70%-88%, 70%-87%, 70%-86%, 70%-85%, 70%-84%, 70%-83%, 70%-82%, 70%-81%, 70%-80%, 75%-90%, 75%-89%, 75%-88%, 75%-87%, 75%-86%, 75%-85%, 75%-84%, 75%-83%, 75%-82%, 75%-81%, 75%-80%, 76%-90%, 76%-89%, 76%-88%, 76%-87%, 76%-86%, 76%-85%, 76%-84%, 76%-83%, 76%-82%, 76%-81%, 76%-80%, 77%-90%, 77%-89%, 77%-88%, 77%-87%, 77%-86%, 77%-85%, 77%-84%, 77%-83%, 77%-82%, 77%-81%, 77%-80%, 78%-90%, 78%-89%, 78%-88%, 78%-87%, 78%-86%, 78%-85%, 78%-84%, 78%-83%, 78%-82%, 78%-81%, 78%-80%, 79%-90%, 79%-89%, 79%-88%, 79%-87%, 79%-86%, 79%-85%, 79%-84%, 79%-83%, 79%-82%, 79%-81%, 79%-80%, 80%-90%, 80%-89%, 80%-88%, 80%-87%, 80%-86%, 80%-85%, 80%-84%, 80%-83%, 80%-82%, 81%-90%, 81%-89%, 81%-88%, 81%-87%, 81%-86%, 81%-85%, 81%-84%, 81%-83%, 81%-82%, 82%-90%, 82%-89%, 82%-88%, 82%-87%, 82%-86%, 82%-85%, 82%-84%, 82%-83%, 83%-90%, 83%-89%, 83%-88%, 83%-87%, 83%-86%, 83%-85%, 83%-84%,

84%-90%, 84%-89%, 84%-88%, 84%-87%, 84%-86%, 84%-85%, 85%-90%, 85%-89%, 85%-88%, 85%-87%, 85%-86%, 86%-90%, 86%-89%, 86%-88%, 86%-87%, 87%-90%, 87%-89%, 87%-88%, 88%-90%, or 88%-89% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject.

[0370] In certain embodiments, a modified oligonucleotide contains a nucleobase sequence complementary to an equal length region within nucleobases 2046-2061 of SEQ ID NO: 1 or within nucleobases 14940-14955 of SEQ ID NO: 2. In certain embodiments, a modified oligonucleotide contains a nucleobase sequence that is at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% complementary to an equal length region within nucleobases 2046-2061 of SEQ ID NO: 1 or within nucleobases 14940-14955 of SEQ ID NO: 2. In certain embodiments, a modified oligonucleotide contains a nucleobase sequence that is 100% complementary to an equal length region within nucleobases 2046-2061 of SEQ ID NO: 1 or within nucleobases 14940-14955 of SEQ ID NO: 2.

[0371] In certain embodiments, the nucleobase sequence of the oligonucleotide, e.g., modified oligonucleotide, containing a nucleobase sequence that is complementary to an equal length target region of an AGT target nucleic acid contains at least 12, at least 13, at least 14, at least 15, or at least 16 contiguous nucleobases of a nucleobase sequence provided in Table 1. In certain embodiments, the nucleobase sequence of the oligonucleotide, e.g., modified oligonucleotide, containing a nucleobase sequence that is complementary to an equal length target region of an AGT target nucleic acid consists of a nucleobase sequence provided in Table 1.

[0372] Table 1: Examples of nucleobase sequences.

SEQ ID NO: 1 Start Site-Stop Site	SEQ ID NO: 2 Start Site-Stop Site	NUCLEOBASE SEQUENCE	SEQ ID NO:
2046-2061	14940-14955	CGCTGATTTGTCCGGG	3
2047-2062	14941-14956	TCGCTGATTTGTCCGG	6
2048-2063	14942-14957	ATCGCTGATTTGTCCG	7
2049-2064	14943-14958	CATCGCTGATTTGTCC	8
2050-2065	14944-14959	ACATCGCTGATTTGTC	9
2051-2066	14945-14960	CACATCGCTGATTTGT	10

[0373] D. Modified Oligonucleotides

[0374] In certain embodiments of compositions and methods described herein comprise an oligomeric agent comprising or consisting of a modified oligonucleotide targeting AGT. Modified oligonucleotides comprise at least one modified nucleoside (comprising a modified sugar moiety and/or a modified nucleobase and/or lacking a nucleobase) and/or at least one modified internucleoside linkage. Examples of certain modified nucleosides and modified internucleoside linkages suitable for use in modified oligonucleotides are described herein. In certain embodiments, modified nucleosides comprising the following modified sugar moieties and/or the following modified nucleobases, and internucleoside linkages comprising the following modifications, may be incorporated into modified oligonucleotides described herein.

[0375] 1. Modified Sugar Moieties

[0376] Modified sugar moieties include modified furanosyl sugar moieties, sugar surrogates (e.g., cyclic sugar surrogates, acyclic sugar surrogates), and sugar mimics. In certain embodiments, modified sugar moieties are non-bicyclic modified furanosyl sugar moieties. In certain embodiments, modified sugar moieties are bicyclic or tricyclic furanosyl sugar moieties. In certain embodiments, modified sugar moieties are sugar surrogates. Sugar surrogates may comprise one or more substitutions corresponding to those of other types of modified sugar moieties.

[0377] In certain embodiments, modified sugar moieties are non-bicyclic modified furanosyl sugar moieties comprising one or more substituent groups including, but not limited to, substituents at the 2', 3', 4', and/or 5' positions. In certain embodiments, the modified furanosyl sugar moiety is a ribosyl sugar moiety that is not an unmodified sugar moiety (*i.e.*, an unmodified RNA or unmodified DNA moiety). In certain embodiments, the modified furanosyl sugar moiety is a xylosyl, lyxosyl, or arabinosyl sugar moiety.

[0378] In certain embodiments, non-bicyclic modified sugar moieties are 2'-substituted sugar moieties and comprise a substituent group at the 2'-position. In certain embodiments one or more non-bridging substituent of non-bicyclic modified sugar moieties is branched. Examples of substituent groups suitable for the 2'-position of modified sugar moieties include but are not limited to: 2'-F, 2'-OCH₃ ("OMe" or "O-methyl"), and 2'-O(CH₂)₂OCH₃ ("MOE" or "O-methoxyethyl"). In certain embodiments, 2'-substituent groups are selected from: halo, allyl, amino, azido, SH, CN, OCN, CF₃, OCF₃, C₁-C₁₀ alkoxy, C₁-C₁₀ substituted alkoxy, C₁-C₁₀ alkyl, C₁-C₁₀ substituted alkyl, S-alkyl, N(R_m)-alkyl, O-alkenyl, S-alkenyl, N(R_m)-alkenyl, O-alkynyl, S-alkynyl, N(R_m)-alkynyl, O-

alkylenyl-O-alkyl, alkynyl, alkaryl, aralkyl, O-alkaryl, O-aralkyl, $\text{O}(\text{CH}_2)_2\text{SCH}_3$, $\text{O}(\text{CH}_2)_2\text{ON}(\text{R}_m)(\text{R}_n)$ or $\text{OCH}_2\text{C}(=\text{O})-\text{N}(\text{R}_m)(\text{R}_n)$, where each R_m and R_n is, independently, H, an amino protecting group, or substituted or unsubstituted C_1 - C_{10} alkyl, $\text{O}(\text{CH}_2)_2\text{ON}(\text{CH}_3)_2$ ("DMAOE"), or $2'\text{-O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$ ("DMAEOE"). Synthetic methods for some of these $2'$ -substituent groups may be found, *e.g.*, in Cook *et al.*, U.S. 6,531,584; Cook *et al.*, U.S. 5,859,221; and Cook *et al.*, U.S. 6,005,087. Certain embodiments of these $2'$ -substituent groups may be further substituted with one or more substituent groups independently selected from: halo, cyano, $\text{OR}^{\text{a}2}$, NO_2 , NH_2 , $\text{NHR}^{\text{a}2}$, $\text{N}(\text{R}^{\text{a}2})_2$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_{10} cycloalkyl, C_6 - C_{10} aryl, heteroaryl, heterocyclyl, C_1 - C_6 alkylene- NH_2 , C_1 - C_6 alkylene- $\text{NHR}^{\text{a}2}$, C_1 - C_6 alkylene- $\text{N}(\text{R}^{\text{a}2})_2$, $\text{C}(\text{O})\text{R}^{\text{a}3}$, $\text{C}(\text{O})\text{OR}^{\text{a}3}$, $\text{C}(\text{O})\text{NHR}^{\text{a}3}$, $\text{C}(\text{O})\text{N}(\text{C}_1\text{-C}_4 \text{ alkyl})\text{R}^{\text{a}3}$, $\text{SR}^{\text{a}3}$, $\text{S}(\text{O})_2\text{R}^{\text{a}3}$, $\text{S}(\text{O})\text{R}^{\text{a}3}$, $\text{NHC}(\text{O})\text{R}^{\text{a}3}$, $\text{N}(\text{C}_1\text{-C}_4 \text{ alkyl})\text{C}(\text{O})\text{R}^{\text{a}3}$, $\text{NHS}(\text{O})\text{R}^{\text{a}3}$, $\text{N}(\text{C}_1\text{-C}_4 \text{ alkyl})\text{S}(\text{O})\text{R}^{\text{a}3}$, $\text{NHS}(\text{O})_2\text{R}^{\text{a}3}$, and $\text{N}(\text{C}_1\text{-C}_4 \text{ alkyl})\text{S}(\text{O})_2\text{R}^{\text{a}3}$; each $\text{R}^{\text{a}2}$ is independently selected from C_2 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_{10} cycloalkyl, C_6 - C_{10} aryl, heteroaryl, and heterocyclyl; each $\text{R}^{\text{a}3}$ is independently hydrogen, OH, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_3 - C_{10} cycloalkyl, C_6 - C_{10} aryl, heteroaryl, or heterocyclyl. In certain embodiments, a sugar moiety comprises two of the above substituents at the $2'$ -position. In certain embodiments, a sugar moiety comprises a $2'$ -fluoro and a second $2'$ -substituent. In certain embodiments, a $2'$ -substituted sugar moiety comprises a non-bridging $2'$ -substituent group selected from: F, NH_2 , N_3 , OCF_3 , OCH_3 , $\text{O}(\text{CH}_2)_3\text{NH}_2$, $\text{CH}_2\text{CH}=\text{CH}_2$, $\text{OCH}_2\text{CH}=\text{CH}_2$, $\text{OCH}_2\text{CH}_2\text{OCH}_3$, $\text{O}(\text{CH}_2)_2\text{SCH}_3$, $\text{O}(\text{CH}_2)_2\text{ON}(\text{R}_m)(\text{R}_n)$, $\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$, and N-substituted acetamide ($\text{OCH}_2\text{C}(=\text{O})-\text{N}(\text{R}_m)(\text{R}_n)$), where each R_m and R_n is, independently, H, an amino protecting group, or substituted or unsubstituted C_1 - C_{10} alkyl. In certain embodiments, a $2'$ -substituted sugar moiety comprises a non-bridging $2'$ -substituent group selected from: F, OCF_3 , OCH_3 , $\text{OCH}_2\text{CH}_2\text{OCH}_3$, $\text{O}(\text{CH}_2)_2\text{SCH}_3$, $\text{O}(\text{CH}_2)_2\text{ON}(\text{CH}_3)_2$, $\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$, $\text{O}(\text{CH}_2)_2\text{ON}(\text{CH}_3)_2$ ("DMAOE"), $\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$ ("DMAEOE"), and $\text{OCH}_2\text{C}(=\text{O})-\text{N}(\text{H})\text{CH}_3$ ("NMA"). In certain embodiments, a $2'$ -substituted sugar moiety comprises a $2'$ -substituent group selected from: F, OCH_3 , and $\text{OCH}_2\text{CH}_2\text{OCH}_3$.

[0379] In certain embodiments, modified furanosyl sugar moieties and nucleosides incorporating such modified furanosyl sugar moieties are further defined by stereochemical configuration. For example, a $2'$ -deoxyfuranosyl sugar moiety (*i.e.*, $2'$ -(H)H furanosyl sugar moiety) may be in seven isomeric configurations other than the naturally occurring β -D-deoxyribose configuration. Such modified sugar moieties are described in, *e.g.*, WO 2020/072991, incorporated by reference herein. A $2'$ -

modified sugar moiety has an additional stereocenter at the 2'-position relative to a 2'-deoxyfuranosyl sugar moiety; therefore, such sugar moieties have a total of sixteen possible stereochemical configurations. Modified furanosyl sugar moieties described herein are in the β -D-ribose stereochemical configuration unless otherwise specified.

[0380] In certain embodiments, non-bicyclic modified sugar moieties comprise a substituent group at the 4'-position. Examples of substituent groups suitable for the 4'-position of modified sugar moieties include, but are not limited to, alkoxy (*e.g.*, methoxy), alkyl, and those described in Manoharan *et al.*, WO 2015/106128, which is incorporated herein by reference.

[0381] In certain embodiments, non-bicyclic modified sugar moieties comprise a substituent group at the 3'-position. Examples of substituent groups suitable for the 3'-position of modified sugar moieties include, but are not limited to, alkoxy (*e.g.*, methoxy), alkyl (*e.g.*, methyl, ethyl).

[0382] In certain embodiments, non-bicyclic modified sugar moieties comprise a substituent group at the 5'-position. Examples of substituent groups suitable for the 5'-position of modified sugar moieties include, but are not limited to, vinyl, alkoxy (*e.g.*, methoxy), alkynyl, allyl, and alkyl (*e.g.*, methyl (*R* or *S*), ethyl (*R* or *S*)).

[0383] In certain embodiments, non-bicyclic modified sugar moieties comprise more than one non-bridging sugar substituent, for example, 2'-F-5'-methyl sugar moieties, such as described in Migawa *et al.*, US 2010/0190837, which is incorporated herein by reference, or alternative 2'- and 5'-modified sugar moieties as described in Rajeev *et al.*, US 2013/0203836, which is incorporated herein by reference.

[0384] Certain modified sugar moieties are bicyclic sugar moieties and comprise a substituent that bridges two atoms of the furanosyl ring to form a second ring. In certain embodiments, the bicyclic sugar moiety comprises a bridge between the 4' and the 2' furanose ring atoms. Examples of such 4' to 2' bridging sugar substituents include, but are not limited to: 4'-CH₂-2', 4'-(CH₂)₂-2', 4'-(CH₂)₃-2', 4'-CH₂-O-2' ("LNA"), 4'-CH₂-S-2', 4'-(CH₂)₂-O-2' ("ENA"), 4'-CH(CH₃)-O-2' (referred to as "constrained ethyl" or "cEt" when in the *S* configuration), 4'-CH₂-O-CH₂-2', 4'-CH₂-N(R)-2', 4'-CH(CH₂OCH₃)-O-2' ("constrained MOE" or "cMOE") and analogs thereof, 4'-C(CH₃)(CH₃)-O-2' and analogs thereof, 4'-CH₂-N(OCH₃)-2' and analogs thereof, 4'-CH₂-O-N(CH₃)-2', 4'-CH₂-C(H)(CH₃)-2', 4'-CH₂-C(=CH₂)-2' and analogs thereof, 4'-C(R_aR_b)-N(R)-O-2', 4'-C(R_aR_b)-O-N(R)-2', 4'-CH₂-O-N(R)-2', and 4'-CH₂-N(R)-O-2', wherein each R, R_a, and R_b is, independently, H, a protecting group, or C₁-C₁₂ alkyl. Representative U.S. patents that teach the preparation of such

bicyclic sugar moieties include, but are not limited to: Imanishi *et al.*, U.S. 7,427,672; Swayze *et al.*, U.S. 7,741,457; Swayze *et al.*, U.S. 8,022,193; Seth *et al.*, U.S. 8,278,283; Prakash *et al.*, U.S. 8,278,425; and Seth *et al.*, U.S. 8,278,426, each of which are incorporated herein by reference.

[0385] In certain embodiments, such 4' to 2' bridges independently comprise from 1 to 4 linked groups independently selected from: $-\text{[C(R}_a\text{)(R}_b\text{)]}_n-$, $-\text{[C(R}_a\text{)(R}_b\text{)]}_n\text{-O-}$, $-\text{C(R}_a\text{)=C(R}_b\text{)-}$, $-\text{C(R}_a\text{)=N-}$, $-\text{C(=NR}_a\text{)-}$, $-\text{C(=O)-}$, $-\text{C(=S)-}$, $-\text{O-}$, $-\text{Si(R}_a\text{)}_2-$, $-\text{S(=O)}_x-$, and $-\text{N(R}_a\text{)-}$; wherein x is 0, 1, or 2; n is 1, 2, 3, or 4; each R_a and R_b is, independently, halo, cyano, OR^{a2} , NO_2 , NH_2 , NHR^{a2} , $\text{N(R}^{a2}\text{)}_2$, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_{10}$ cycloalkyl, $\text{C}_6\text{-C}_{10}$ aryl, heteroaryl, heterocyclyl, $\text{C}_1\text{-C}_6$ alkylene- NH_2 , $\text{C}_1\text{-C}_6$ alkylene- NHR^{a2} , $\text{C}_1\text{-C}_6$ alkylene- $\text{N(R}^{a2}\text{)}_2$, C(O)R^{a3} , C(O)OR^{a3} , C(O)NHR^{a3} , $\text{C(O)N(C}_1\text{-C}_4\text{ alkyl)R}^{a3}$, SR^{a3} , $\text{S(O)}_2\text{R}^{a3}$, S(O)R^{a3} , NHC(O)R^{a3} , $\text{N(C}_1\text{-C}_4\text{ alkyl)C(O)R}^{a3}$, NHS(O)R^{a3} , $\text{N(C}_1\text{-C}_4\text{ alkyl)S(O)R}^{a3}$, $\text{NHS(O)}_2\text{R}^{a3}$, and $\text{N(C}_1\text{-C}_4\text{ alkyl)S(O)}_2\text{R}^{a3}$; each R^{a2} is independently selected from $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_{10}$ cycloalkyl, $\text{C}_6\text{-C}_{10}$ aryl, heteroaryl, and heterocyclyl; each R^{a3} is independently hydrogen, OH, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_3\text{-C}_{10}$ cycloalkyl, $\text{C}_6\text{-C}_{10}$ aryl, heteroaryl, or heterocyclyl.

[0386] In certain embodiments, the bicyclic sugar moiety comprises a bridge between the 5' and the 3' furanose ring atoms. Examples of such 5' to 3' bridging sugar substituents include, but are not limited to, 5'-(CH_2)₂-3' (bcDNA), 5'-(CH_2)₃-3' (bc^{4,3}DNA), 5'- C(F)=CH-CH_2 -3', and 5'- $\text{CH}_2\text{-CHQ-}$ 3', wherein Q is an attachment to an internucleoside linkage. Additional bicyclic sugar moieties are known in the art, see, for example: Wan, *et al.*, *J. Medicinal Chemistry*, 2016, 59, 9645-9667; Wengel *et al.*, U.S. 8,080,644; Ramasamy *et al.*, U.S. 6,525,191; Seth *et al.*, U.S. 7,547,684; and Seth *et al.*, U.S. 7,666,854, which are each incorporated herein by reference. In certain embodiments, bicyclic sugar moieties and nucleosides incorporating such bicyclic sugar moieties are further defined by stereochemical configuration. For example, an LNA nucleoside (described herein) may be in the α -L configuration or in the β -D configuration. α -L-methyleneoxy (4'- $\text{CH}_2\text{-O-2'}$) or α -L-LNA bicyclic nucleosides have been incorporated into oligonucleotides that showed antisense activity (Frieden *et al. Nucleic Acids Res.* 2003, 21, 6365-6372). The addition of locked nucleic acids to siRNAs has been shown, in certain studies, to increase siRNA stability in serum, and to reduce off-target effects (Elmén, J. *et al. Nucleic Acids Res.* 2005, 33(1), 439-447; Mook, O. R. *et al. Mol. Canc. Ther.* 2007, 6(3), 833-843; Grunweller, A. *et al. Nucleic Acids Res.* 2003, 31(12), 3185-3193). Herein, general descriptions of bicyclic nucleosides include both stereochemical configurations. When the positions of specific

bicyclic nucleosides (*e.g.*, LNA or cEt) are identified in exemplified embodiments herein, they are in the β -D stereochemical configuration, unless otherwise specified.

[0387] In certain embodiments, modified sugar moieties comprise one or more non-bridging sugar substituent and one or more bridging sugar substituent (*e.g.*, 5'-substituted and 4'-2' bridged sugars).

[0388] In certain embodiments, modified sugar moieties are sugar surrogates, selected from cyclic sugar surrogates and acyclic sugar surrogates.

[0389] In certain embodiments, the oxygen atom of the sugar moiety is replaced, *e.g.*, with a sulfur, carbon or nitrogen atom (X is S, C(R₁R₂), or N(R₃)). In certain such embodiments, such modified sugar moieties also comprise bridging and/or non-bridging substituents as described herein. For example, certain sugar surrogates comprise a 4'-sulfur atom and a substitution at the 2'-position and/or the 5' position.

[0390] In certain embodiments, sugar surrogates comprise rings having other than 5 atoms. For example, in certain embodiments, a sugar surrogate comprises a six-membered tetrahydropyran ("THP"), where X is O-C(R₁R₂), p is 1, Q is CH, Z is C(G₁G₂), and m is 0. Such tetrahydropyrans may be further modified or substituted. Nucleosides comprising such modified tetrahydropyrans include but are not limited to hexitol nucleic acid ("HNA"), altritol nucleic acid (G₁=OH; G₂=H; "ANA"), and fluoro HNA "FHNA", see *e.g.*, Egli, M. *et al. J. Am. Chem. Soc.* 2011, 133(41), 16642-16649; Swayze *et al.*, U.S. 8,088,904; and Swayze *et al.*, U.S. 8,440,803; FHNA can also be referred to as a F-THP or 3'-fluoro tetrahydropyran or 3'-FHNA), which are each incorporated herein by reference.

[0391] In certain embodiments, sugar surrogates comprise rings having more than 5 atoms and more than one heteroatom. For example, nucleosides comprising morpholino sugar moieties and their use in oligonucleotides have been reported. As used here, the term "morpholino" means a sugar surrogate having Formula Ia, above, wherein X is O, Y and Z are each CH₂, and Q is N. In certain embodiments, a morpholino is modified, for example by adding or altering various substituent groups from the above morpholino structure. Such sugar surrogates are referred to herein as "modified morpholinos."

[0392] In certain embodiments, sugar surrogates are acyclic sugar surrogates. In certain embodiments, acyclic sugar surrogates are the "unlocked" sugar structure of UNA ("unlocked nucleic acid") nucleosides. Representative U.S. publications that teach the preparation of UNA include, but are not limited to, U.S. Patent Publication No. 2011/0313020. In certain embodiments, acyclic sugar surrogates are the glycerol as found in GNA ("glycol nucleic acid") nucleosides. Further acyclic sugar

surrogates include those described in Manoharan *et al.*, U.S. 10,913,767; US patent publication US 2021/0238595; and PCT publication WO 2023/109940.

[0393] In certain embodiments, modified oligonucleotides include one or more sugar mimic, in which a group of atoms other than a “furanosyl sugar moiety” or a “sugar surrogate” form the portion of a nucleoside corresponding to the β -D-ribose sugar in RNA. In certain embodiments, a sugar mimic is a portion of the backbone of a peptide nucleic acid, while the remainder of the backbone of the peptide nucleic acid is an internucleoside linkage. Representative U.S. patents that teach the preparation of PNA compounds include, but are not limited to, U.S. Patent Nos. 5,539,082; 5,714,331; and 5,719,262.

[0394] 2. Modified Nucleobases

[0395] In certain embodiments, modified oligonucleotides comprise one or more nucleoside comprising an unmodified nucleobase. In certain embodiments, modified oligonucleotides comprise one or more nucleoside comprising a modified nucleobase. In certain embodiments, modified oligonucleotides comprise one or more nucleoside that does not comprise a nucleobase, referred to as an abasic nucleoside. In certain embodiments, modified oligonucleotides contain no abasic nucleosides. In certain embodiments, modified oligonucleotides comprise one or more inosine nucleosides (*i.e.*, nucleosides comprising a hypoxanthine nucleobase). An “unmodified nucleobase” is unmodified adenine (A), unmodified thymine (T), unmodified cytosine (C), unmodified uracil (U), or unmodified guanine (G). A modified nucleobase is a group of atoms other than unmodified A, T, C, U, or G capable of pairing with at least one other nucleobase. A 5-methylcytosine is an example of a modified nucleobase. A universal base is a modified nucleobase that can pair with any one of the five unmodified nucleobases, *e.g.*, inosine (I).

[0396] In certain embodiments, modified nucleobases of a modified oligonucleotide are selected from: 5-substituted pyrimidines, 6-azapyrimidines, alkyl or alkynyl substituted pyrimidines, alkyl substituted purines, and N-2, N-6, and O-6 substituted purines. In certain embodiments, modified nucleobases are selected from: 5-methylcytosine, hypoxanthine, 1-methylpseudouridine, 2-aminopropyladenine, 5-hydroxymethyl cytosine, xanthine, 2-aminoadenine, 6-N-methylguanine, 6-N-methyladenine, 2-propyladenine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-propynyl ($-C\equiv C-CH_3$) uracil, 5-propynylcytosine, 6-azouracil, 6-azocytosine, 6-azothymine, 5-ribosyluracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl, 8-aza and other 8-substituted purines, 5-halo (particularly 5-bromo), 5-trifluoromethyl, 5-halouracil, and 5-

halocytosine, 7-methylguanine, 7-methyladenine, 2-F-adenine, 2-aminoadenine, 7-deazaguanine, 7-deazaadenine, 3-deazaguanine, 3-deazaadenine, 6-N-benzoyladenine, 2-N-isobutyrylguanine, 4-N-benzoylcytosine, 4-N-benzoyluracil, 5-methyl 4-N-benzoylcytosine, 5-methyl 4-N-benzoyluracil, universal bases, hydrophobic bases, promiscuous bases, size-expanded bases, and fluorinated bases. Further modified nucleobases include tricyclic pyrimidines, such as 1,3-diazaphenoxazine-2-one, 1,3-diazaphenothiazine-2-one, and 9-(2-aminoethoxy)-1,3-diazaphenoxazine-2-one (G-clamp). Modified nucleobases may also include those in which the purine or pyrimidine base is replaced with other heterocycles, for example, 7-deaza-adenine, 7-deazaguanosine, 2-aminopyridine, and 2-pyridone. Further nucleobases include those disclosed in Englisch, U. *et al.*, *Angew. Chem. Int. Ed.* 1991, 30, 613; Sanghvi, Y.S., Chapter 15, *Antisense Research and Applications*, Crooke, S. T. and Lebleu, B., Eds., CRC Press, 1993, 273-288; and those disclosed in Chapters 6 and 15, *Antisense Drug Technology*, Crooke S.T., Ed., CRC Press, 2008, 163-166 and 442-443.

[0397] Preparation of certain of the above noted modified nucleobases, as well as other modified nucleobases are known in the art and can be readily identified in publications that include without limitation, Rogers *et al.*, U.S. 5,134,066 ; Benner *et al.*, U.S. 5,432,272; Matteucci *et al.*, U.S. 5,502,177 ; Froehler *et al.*, U.S. 5,594,121 ; and Cook *et al.*, U.S. 5,681,941.

[0398] In certain embodiments, each nucleobase of a modified oligonucleotide is selected from unmodified A, unmodified G, unmodified C, unmodified T, unmodified U, and ¹³C. In certain embodiments, each nucleobase of a modified oligonucleotide is selected from unmodified A, unmodified G, unmodified C, unmodified T, unmodified U, ¹³C, or hypoxanthine. In certain embodiments, there are no modified nucleobases in a modified oligonucleotide and each nucleobase of a modified oligonucleotide is selected from unmodified A, unmodified G, unmodified C, unmodified T, and unmodified U.

[0399] 3. Modified Internucleoside Linkages

[0400] In certain embodiments, oligomeric agents provided herein comprise or consist of a modified oligonucleotide comprising at least one modified internucleoside linkage. The naturally occurring internucleoside linkage of RNA and DNA is a 3' to 5' phosphodiester linkage. Herein, all internucleoside linkages between furanosyl sugar moieties are 3' to 5' internucleoside linkages unless otherwise indicated. In certain embodiments, nucleosides of modified oligonucleotides are linked together using one or more modified internucleoside linkages. The two main classes of internucleoside linkages are defined by the presence or absence of a phosphorus atom. Representative

phosphorus-containing internucleoside linkages include but are not limited to phosphates, which contain a phosphodiester bond (“P=O”) (also referred to as unmodified linkages), phosphotriesters, methylphosphonates, phosphoramidates, phosphorothioates (“P=S”), and phosphorodithioates (“HS-P=S”). Representative non-phosphorus containing internucleoside linkages include but are not limited to methylenemethylimino (-CH₂-N(CH₃)-O-CH₂-), thiodiester, thionocarbamate (-O-C(=O)(NH)-S-), siloxane (-O-SiH₂-O-), and N,N'-dimethylhydrazine (-CH₂-N(CH₃)-N(CH₃)-). Modified internucleoside linkages, compared to naturally occurring phosphodiester linkages, may be used to alter, typically increase, nuclease resistance of the oligonucleotide.

[0401] In certain embodiments, a modified internucleoside linkage is any of those described in WO 2021/030778, incorporated by reference herein. Certain internucleoside linkages having reduced charge (referred to as “neutral internucleoside linkages”) have been described. Such neutral internucleoside linkages include, without limitation, phosphotriesters, methylphosphonates, MMI (3'-CH₂-N(CH₃)-O-5'), amide-3 (3'-CH₂-C(=O)-N(H)-5'), amide-4 (3'-CH₂-N(H)-C(=O)-5'), formacetal (3'-O-CH₂-O-5'), methoxypropyl (MOP) (see US 9,926,556), and thioformacetal (3'-S-CH₂-O-5'). Further neutral internucleoside linkages include nonionic linkages comprising siloxane (dialkylsiloxane), carboxylate ester, carboxamide, sulfide, sulfonate ester and amides (See for example: *Carbohydrate Modifications in Antisense Research*; Y.S. Sanghvi and P.D. Cook, Eds., ACS Symposium Series 580; Chapters 3 and 4, 40-65). Further neutral internucleoside linkages include nonionic linkages comprising mixed N, O, S and CH₂ component parts.

[0402] In certain embodiments, a modified oligonucleotide comprises an internucleoside linkage comprising a triazole, alkyne, or cyclic guanidine moiety. In certain embodiments, internucleoside linkages are not 3'-to-5' internucleoside linkages.

[0403] In certain embodiments, modified oligonucleotides comprise one or more inverted nucleoside. In certain embodiments, an inverted nucleoside is terminal (*i.e.*, the last nucleoside on one end of an oligonucleotide) and so only one internucleoside linkage depicted above will be present. In certain embodiments, additional features (*e.g.*, a conjugate group) are attached to the inverted nucleoside. Such terminal inverted nucleosides may be attached to either or both ends of an oligonucleotide. In certain embodiments, inverted nucleosides lack a nucleobase (are abasic nucleosides). In certain such embodiments, additional features (*e.g.*, a conjugate group) are attached to the inverted abasic nucleoside. A terminal inverted nucleoside may be attached to either or both ends of an oligonucleotide.

[0404] In certain embodiments, nucleosides are linked 2' to 5' rather than the 3' to 5' linkage.

[0405] In certain embodiments, a bicyclic sugar moiety may be linked via an atom on the non-furanosyl ring. In certain such embodiments, a bicyclic sugar moiety is linked 7' to 5'.

[0406] In certain embodiments, internucleoside linkages have at least one chiral center. In such embodiments, a chiral atom can be prepared as a racemic mixture, or as separate enantiomers. Representative internucleoside linkages having a chiral center include but are not limited to alkylphosphonates, mesyl phosphoramidates, and phosphorothioates.

[0407] D. Motifs

[0408] In certain embodiments, modified oligonucleotides comprise one or more modified nucleosides comprising a modified sugar moiety. In certain embodiments, modified oligonucleotides comprise one or more modified nucleosides comprising a modified nucleobase. In certain embodiments, modified oligonucleotides comprise one or more modified internucleoside linkage. In certain embodiments, the modified, unmodified, and differently modified sugar moieties, nucleobases, and/or internucleoside linkages of a modified oligonucleotide define a pattern or motif. In certain embodiments, the patterns of sugar moieties, nucleobases, and internucleoside linkages are each independent of one another. Thus, a modified oligonucleotide may be described by its sugar motif, nucleobase motif, and/or internucleoside linkage motif (as used herein, nucleobase motif describes the modifications to the nucleobases independent of the nucleobase sequence).

[0409] 1. Sugar Motifs

[0410] In certain embodiments, oligonucleotides comprise one or more type of modified sugar and/or unmodified sugar moiety arranged along the oligonucleotide or region thereof in a defined pattern or sugar motif. In certain instances, a sugar motif includes but is not limited to any of the sugar modifications discussed herein. In certain embodiments, the sugar moiety of at least one nucleoside of a modified oligonucleotide is a modified sugar moiety. In certain embodiments, modified oligonucleotides comprise or consist of a region having a fully modified sugar motif. In such embodiments, each nucleoside of the fully modified region of the modified oligonucleotide comprises a modified sugar moiety. In certain embodiments, each nucleoside of the entire modified oligonucleotide comprises a modified sugar moiety and the oligonucleotide is referred to as a fully modified oligonucleotide. In certain embodiments, modified oligonucleotides comprise or consist of a region having a fully modified sugar motif, wherein each nucleoside within the fully modified region comprises the same modified sugar moiety, referred to herein as a uniformly modified sugar motif.

In certain embodiments, each nucleoside of a uniformly modified oligonucleotide is a 2'-substituted nucleoside comprising the same 2'-substituent. In certain embodiments, every other nucleoside of a fully modified oligonucleotide comprises the same 2'-substituent, resulting in alternating 2'-substituents. In certain embodiments, at least one nucleoside of a modified oligonucleotide comprises a 2'-OMe sugar moiety (*i.e.*, is a 2'-OMe modified nucleoside). In certain embodiments, at least one nucleoside of a modified oligonucleotide comprises a 2'-F sugar moiety (*i.e.*, is a 2'-F modified nucleoside). In certain embodiments, at least one nucleoside of a modified oligonucleotide comprises a cEt sugar moiety. In certain embodiments, a sugar moiety of an antisense oligonucleotide is modified, wherein the modified nucleoside comprises a sugar moiety selected from 2'-F, 2'-MOE, 2'-OMe, 2'-NMA, 2'-deoxy, cEt, and FHNA.

[0411] In certain embodiments, at least one nucleoside of a modified oligonucleotide comprises a 2'-deoxy sugar moiety. In certain embodiments, a modified oligonucleotide comprises a deoxy region. In certain embodiments, the deoxy region consists of 5-12 or 7-12 linked nucleosides. In certain embodiments, the deoxy region consists of 6, 7, 8, 9, 10, or 6-10 linked nucleosides. In certain embodiments, at least one nucleoside within the deoxy region comprises a modified sugar moiety. In certain embodiments, each nucleoside of the deoxy region is a deoxynucleoside. In certain embodiments, each nucleoside of the deoxy region is a 2'- β -D-deoxynucleoside. In certain embodiments, the deoxy region is flanked on the 5'-side by a 5'-region consisting of linked 5'-region nucleosides and on the 3'-side by a 3'-region consisting of linked 3'-region nucleosides; wherein the 3'-most nucleoside of the 5'-region comprises a modified sugar moiety and the 5'-most nucleoside of the 3'-region is comprises a modified sugar moiety. In certain embodiments, the sugar moiety of the 3'-most nucleoside of the 5'-region and the sugar moiety of the 5'-most nucleoside of the 3'-region each differ from the sugar moiety of the respective adjacent nucleoside of the deoxy region, thus defining the boundary between the 5'-region, the deoxy region, and the 3'-region. In certain embodiments, each nucleoside of the 5'-region and each nucleoside of the 3'-region comprises a modified sugar moiety.

[0412] In certain embodiments, modified oligonucleotides have a sugar motif from 5' to 3': eekddddddekkke; wherein each “d” represents a 2'- β -D-deoxyribose sugar moiety, each “k” represents a cEt sugar moiety and each “e” represents a 2'-MOE sugar moiety.

[0413] 2. Nucleobase Motifs

[0414] In certain embodiments, oligonucleotides comprise modified and/or unmodified nucleobases arranged along the oligonucleotide or region thereof in a defined pattern or motif. In certain embodiments, at least one nucleobase is modified. In certain embodiments, none of the nucleobases are modified. In certain embodiments, at least one purine and/or at least pyrimidine is modified. In certain embodiments, at least one adenine is modified. In certain embodiments, at least one guanine is modified. In certain embodiments, at least one thymine is modified. In certain embodiments, at least one uracil is modified. In certain embodiments, at least one cytosine is modified. In certain embodiments, at least one of the cytosine nucleobases in a modified oligonucleotide is 5-methylcytosine. In certain embodiments, all of the cytosine nucleobases are 5-methylcytosines and all of the other nucleobases of the modified oligonucleotide are unmodified nucleobases. In certain embodiments, one or two of the cytosine nucleobases are 5-methylcytosines and all of the other nucleobases of the modified oligonucleotide are unmodified nucleobases.

[0415] 3. Internucleoside Linkage Motifs

[0416] In certain embodiments, oligonucleotides comprise modified and unmodified internucleoside linkages arranged along the oligonucleotide or region thereof in a defined pattern or motif. In certain embodiments, each internucleoside linkage is a phosphodiester internucleoside linkage. In certain embodiments, each internucleoside linkage of a modified oligonucleotide is a phosphorothioate internucleoside linkage. In certain embodiments, each internucleoside linkage of a modified oligonucleotide is independently selected from a phosphorothioate internucleoside linkage, a mesyl phosphoramidate internucleoside linkage, and a phosphodiester internucleoside linkage. In certain embodiments, each internucleoside linkage of a modified oligonucleotide is independently selected from a phosphorothioate internucleoside linkage and a phosphodiester internucleoside linkage. In certain embodiments, each internucleoside linkage of a modified oligonucleotide is independently selected from a mesyl phosphoramidate internucleoside linkage and a phosphorothioate internucleoside linkage. In certain embodiments, each phosphorothioate internucleoside linkage is independently selected from a stereorandom phosphorothioate, a (*Sp*) phosphorothioate, and a (*Rp*) phosphorothioate. In certain embodiments, each mesyl phosphoramidate internucleoside linkage is independently selected from a stereorandom mesyl phosphoramidate, a (*Sp*) mesyl phosphoramidate, and a (*Rp*) mesyl phosphoramidate. In certain embodiments an antisense oligonucleotide has an internucleoside linkage motif (from 5' to 3') of: soosssssssos, wherein each 'o' represents a

phosphodiester internucleoside linkage and each 's' represents a phosphorothioate internucleoside linkage.

[0417] In certain embodiments, a modified oligonucleotide is characterized by sequence, modification motif(s) and overall length. In certain embodiments, such parameters are each independent of one another. Thus, unless otherwise indicated, each internucleoside linkage of a modified oligonucleotide having one or more modified sugar moiety and/or sugar motif, independently, is modified or unmodified and may or may not follow the modification pattern of the sugar modifications or sugar motif. For example, internucleoside linkages within a region of a modified oligonucleotide comprising certain sugar modifications may be the same or different from one another and may be the same or different from the internucleoside linkages of the region of the modified oligonucleotide comprising different sugar modifications. Likewise, such modified oligonucleotides may comprise one or more modified nucleobase independent of the pattern of the sugar modifications or sugar motif and independent of the internucleoside linkages or internucleoside linkage motif. Unless specifically indicated, all modifications are independent of nucleobase sequence. Furthermore, each modification, whether internucleoside linkage, modified sugar moiety, or modified nucleobase, of a modified oligonucleotide, e.g., a modified antisense oligonucleotide, is independent of each modification of a paired oligonucleotide, e.g., sense oligonucleotide, unless specifically indicated otherwise.

[0418] E. Antisense Oligonucleotides

[0419] In certain embodiments, an oligomeric agent comprises a modified oligonucleotide that is an antisense oligonucleotide, e.g., modified antisense oligonucleotide; wherein such oligomeric agent is an antisense agent. In certain embodiments, an oligomeric agent comprises a modified single-stranded antisense oligonucleotide. In certain embodiments, the oligomeric agent is an RNase H agent. In certain embodiments, a single-stranded oligonucleotide, e.g., modified oligonucleotide, comprises at least 12, at least 13, at least 14, at least 15, or at least 16 contiguous nucleosides complementary to an equal length region within nucleobases 2046-2061 of SEQ ID NO: 1 or within nucleobases 14940-14955 of SEQ ID NO: 2. In certain embodiments, the single-stranded oligonucleotide, e.g., modified oligonucleotide, consists of 16 to 25, 16 to 23, 16 to 20, 16 to 18, 16 to 17, or 16 linked nucleosides, wherein at least 12, at least 13, at least 14, at least 15, or at least 16 contiguous nucleosides complementary to an equal length region within nucleobases 2046-2061 of SEQ ID NO: 1 or within nucleobases 14940-14955 of SEQ ID NO: 2.

[0420] In certain embodiments, an oligomeric agent comprising a modified oligonucleotide, e.g., modified antisense oligonucleotide is a duplex wherein a modified antisense oligonucleotide is paired with a second oligonucleotide, e.g., a second modified oligonucleotide, to form an oligomeric duplex. In certain embodiments, an oligomeric duplex comprises a first modified oligonucleotide comprising at least 12, at least 13, at least 14, at least 15, or at least 16 contiguous nucleosides complementary to an equal length region within nucleobases 2046-2061 of SEQ ID NO: 1 or within nucleobases 14940-14955 of SEQ ID NO: 2. In certain embodiments, an oligomeric duplex comprises a first modified oligonucleotide comprising modified oligonucleotide consisting of 16 to 25, 16 to 23, 16 to 20, 16 to 18, 16 to 17, or 16 linked nucleosides, wherein at least 12, at least 13, at least 14, at least 15, or at least 16 contiguous nucleosides complementary to an equal length region within nucleobases 2046-2061 of SEQ ID NO: 1 or within nucleobases 14940-14955 of SEQ ID NO: 2. In certain embodiments, an oligomeric agent comprises an oligomeric duplex, wherein the oligomeric agent comprises or consists of: (1) a first modified oligonucleotide (e.g., an antisense oligonucleotide), (2) a second oligonucleotide (e.g., a sense oligonucleotide), and (3) optionally a terminal group and/or a conjugate group. Either or both oligonucleotides of an oligomeric duplex may be linked to a conjugate group. Either or both oligonucleotides of an oligomeric duplex may comprise a terminal group. Each oligonucleotide of an oligomeric duplex may include non-complementary or unpaired overhanging nucleosides. In certain embodiments, the nucleobase of the non-complementary or unpaired overhanging nucleosides is adenine or thymine. In certain embodiments, the two oligonucleotides have at least one mismatch relative to one another. In certain embodiments, a first modified oligonucleotide of an oligomeric duplex is an antisense oligonucleotide and a second oligonucleotide of the oligomeric duplex is a sense oligonucleotide and the oligomeric duplex is an antisense agent. In certain embodiments, the antisense activity of the oligomeric duplex involves loading of the antisense oligonucleotide into an RNA-induced silencing complex (RISC), ultimately resulting in cleavage of the target nucleic acid. For example, certain antisense oligonucleotides result in cleavage of the target nucleic acid by Argonaute. Antisense agents that comprise an antisense oligonucleotide that is loaded into RISC are RNAi agents. RNAi agents may be double-stranded (siRNA or dsRNAi) or single-stranded (ssRNA). In certain embodiments, RNAi agents are capable of RISC-mediated modulation of a target nucleic acid in a cell.

[0421] F. Antisense Activity

[0422] Antisense activities may be observed directly or indirectly. In certain embodiments, antisense activity involves a decrease in an amount or level of AGT RNA and/or AGT protein (e.g., human AGT RNA and/or human AGT protein) in a cell or subject. Methods for detecting a change in an amount or level of AGT RNA and/or AGT protein in a cell or subject include, for example, measuring the amount of AGT RNA and/or AGT protein in a cell or in a sample from a subject (e.g., blood, plasma, or serum) at different times or under different conditions and comparing the amounts, which, if different, indicates a change in the amount or level of AGT RNA and/or AGT protein. For example, the amount or level of AGT RNA and/or AGT protein in a cell or a sample from a subject may be measured before administering an oligomeric agent described herein, e.g., ION904 (e.g., baseline amount or level of AGT RNA and/or AGT protein), and the amount compared to the level or amount of AGT RNA and/or AGT protein measured after administering an oligomeric agent described herein, e.g., ION904. Methods of measuring AGT RNA and AGT protein are known in the art and/or described herein (see, e.g., International Application PCT/US2021/059896 publication WO2022/109139). For example, AGT RNA (e.g., human AGT RNA) can be measured by extracting RNA from cells or tissues and performing real-time PCR analysis using a primer probe set (e.g., human AGT primer probe). One such human AGT primer probe set is RTS3721 (forward sequence CCCTGATGGGAGCCAGTGT, designated herein as SEQ ID NO: 11; reverse sequence AGCAGGGAGAAGCCCTTCA, designated herein as SEQ ID NO: 12; and probe sequence CCCTGGCTTTCAACACCTACGTCCACTX, where X is a fluorescent label, designated herein as SEQ ID NO: 13). Results can be normalized to total RNA content, for example, measure by RIBOGREEN[®] and/or to GAPDH (e.g., human GAPDH) using PCR. AGT protein (e.g., human AGT protein) in a sample, e.g., plasma, can be measured, e.g., using an ELISA method. For example, ELISA kits are available for performing ELISA measurements (Human Total Angiotensinogen Assay Kit, IBL (Immuno-Biological Laboratories Co., Ltd.), Cat #27412) according to the manufacturer's instructions.

[0423] G. Conjugate and Terminal Groups

[0424] In certain embodiments, provided herein are oligomeric compounds comprising one or more modified oligonucleotide and one or more conjugate groups. In certain embodiments, an oligomeric compound optionally further comprises one or more terminal groups. Conjugate groups comprise or consist of a conjugate moiety and a conjugate linker. A conjugate group may be attached at the 3' end and/or the 5' end of an oligonucleotide and/or at any internal position. In certain embodiments,

conjugate groups are attached through a modified sugar moiety or a modified internucleoside linkage. In certain embodiments, oligomeric compounds comprise a modified oligonucleotide, a cell-targeting moiety, and a conjugate linker.

[0425] 1. Conjugate Groups

[0426] In certain embodiments, a conjugate group comprises a conjugate moiety and a conjugate linker.

[0427] a. Conjugate Moieties

[0428] In certain embodiments, a conjugate moiety modifies one or more properties of an attached oligonucleotide, including but not limited to pharmacodynamics, pharmacokinetics, stability, binding, absorption, tissue distribution, cellular distribution, cellular uptake, charge and clearance.

In certain embodiments, a conjugate moiety imparts a new property on the attached oligonucleotide.

[0429] In certain embodiments, a conjugate moiety comprises or consists of a cell-targeting moiety. In certain embodiments, a cell-targeting moiety is capable of binding the cell-surface receptor or the cell-surface moiety. In certain embodiments, an agent comprising a cell-targeting moiety is capable of being internalized when it interacts with or binds the cell-surface receptor or the cell-surface moiety. In certain embodiments, a cell-targeting moiety comprises a liver cell targeting moiety or a liver cell ligand. In certain embodiments, a liver cell-targeting moiety consists of a cell-targeting moiety having affinity for the hepatic asialoglycoprotein receptor (ASGP-R). In certain embodiments, the cell-targeting moiety comprises more than one ligand, and each ligand has affinity for the ASGP-R. In certain embodiments, each ligand is a carbohydrate. In certain embodiments, each ligand is independently selected from galactose, N-acetyl galactosamine (GalNAc), mannose, glucose, glucosamine, and fucose.

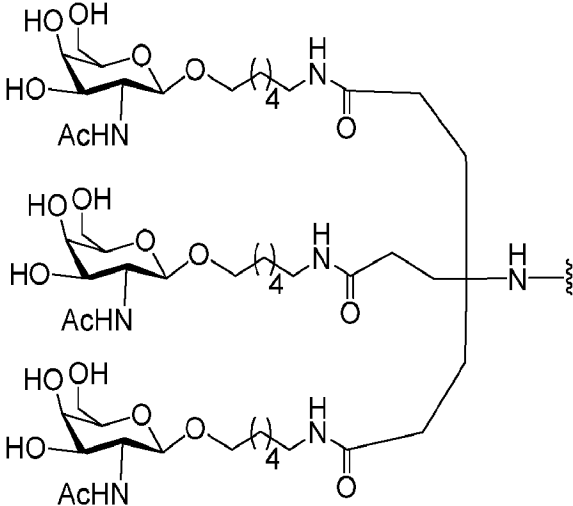
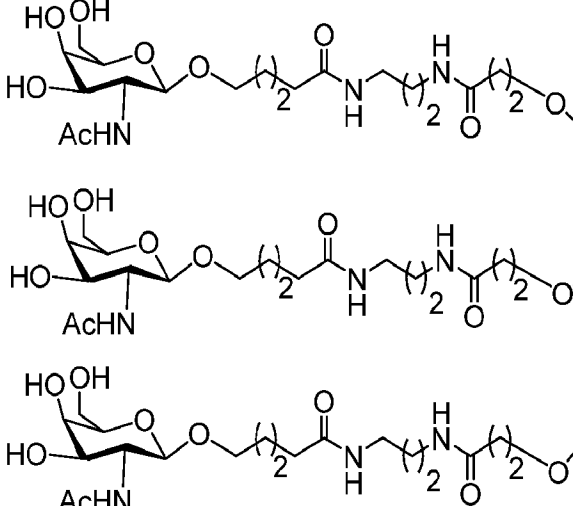
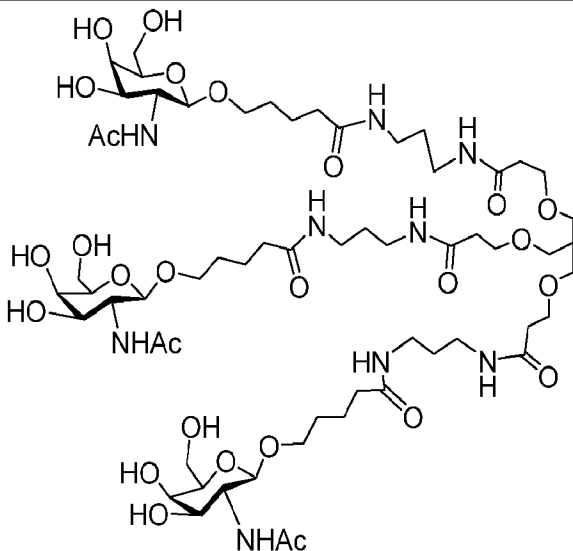
[0430] In certain embodiments, each ligand of a cell-targeting moiety is a carbohydrate, carbohydrate derivative, modified carbohydrate, polysaccharide, modified polysaccharide, or polysaccharide derivative. In certain embodiments, the conjugate group comprises a carbohydrate cluster (*see, e.g.,* Maier et al., “Synthesis of Antisense Oligonucleotides Conjugated to a Multivalent Carbohydrate Cluster for Cellular Targeting,” *Bioconjugate Chemistry*, 2003, 14, 18-29 or Rensen et al., “Design and Synthesis of Novel N-Acetylgalactosamine-Terminated Glycolipids for Targeting of Lipoproteins to the Hepatic Asialoglycoprotein Receptor,” *J. Med. Chem.* 2004, 47, 5798-5808). In certain embodiments, each ligand is an amino sugar or a thio sugar. For example, amino sugars may be selected from any number of compounds known in the art, such as sialic acid, α -D-galactosamine, β -

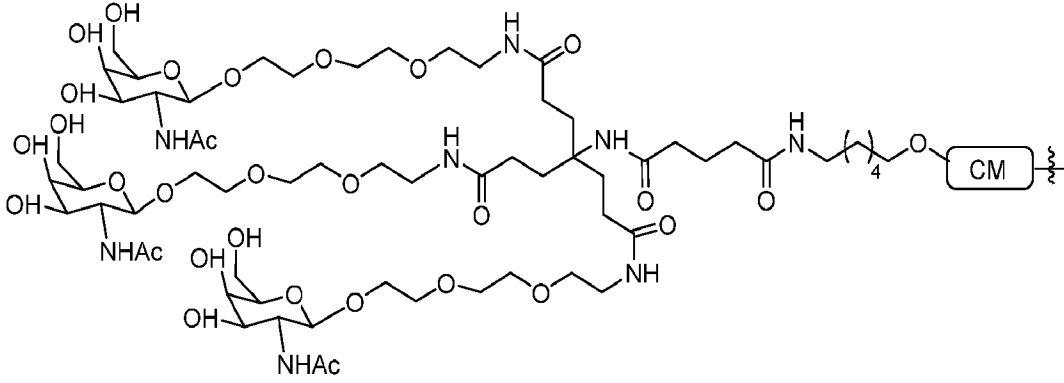
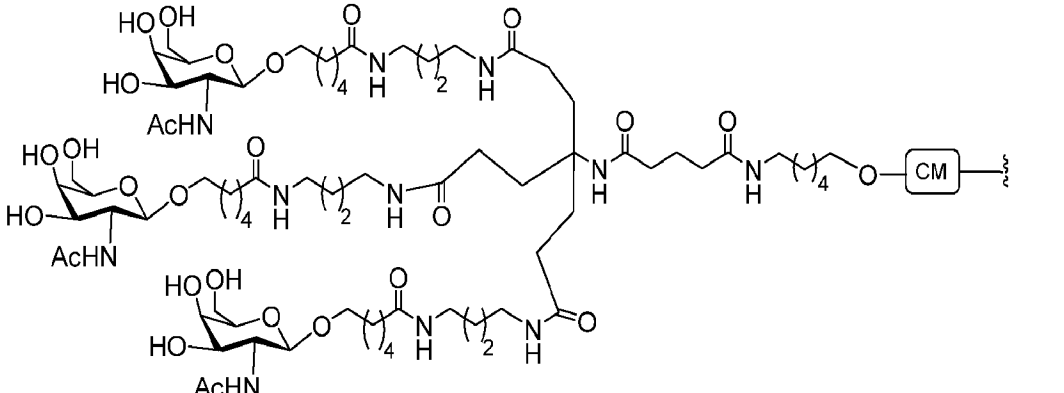
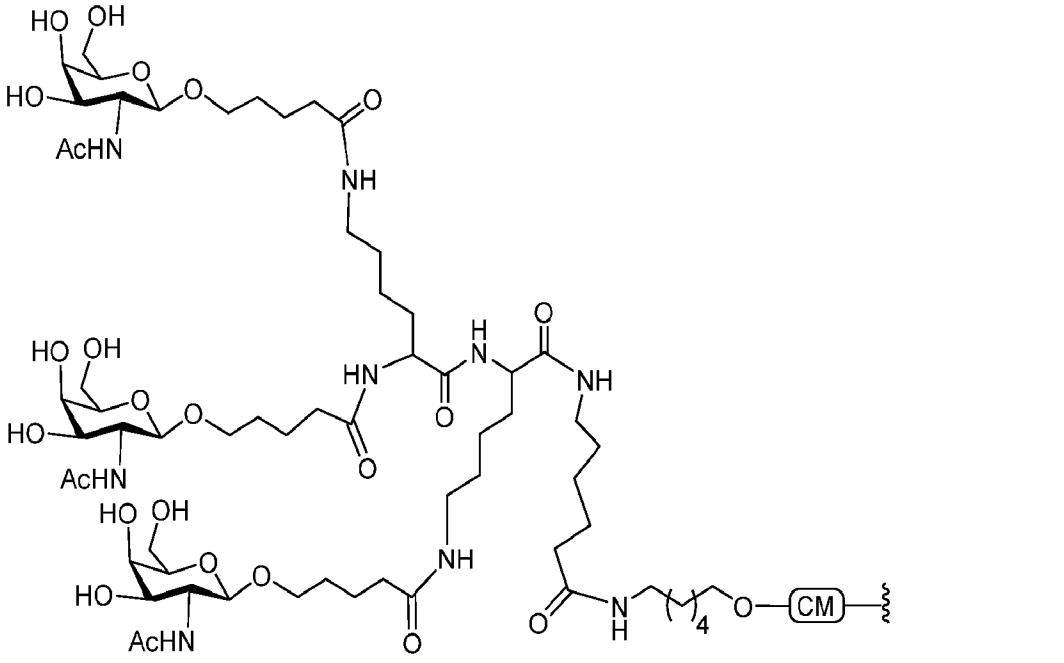
muramic acid, 2-deoxy-2-methylamino-L-glucopyranose, 4,6-dideoxy-4-formamido-2,3-di-*O*-methyl-D-mannopyranose, 2-deoxy-2-sulfoamino-D-glucopyranose and *N*-sulfo-D-glucosamine, and *N*-glycoloyl- α -neuraminic acid. For example, thio sugars may be selected from 5-Thio- β -D-glucopyranose, methyl 2,3,4-tri-*O*-acetyl-1-thio-6-*O*-trityl- α -D-glucopyranoside, 4-thio- β -D-galactopyranose, and ethyl 3,4,6,7-tetra-*O*-acetyl-2-deoxy-1,5-dithio- α -D-*gluco*-heptopyranoside.

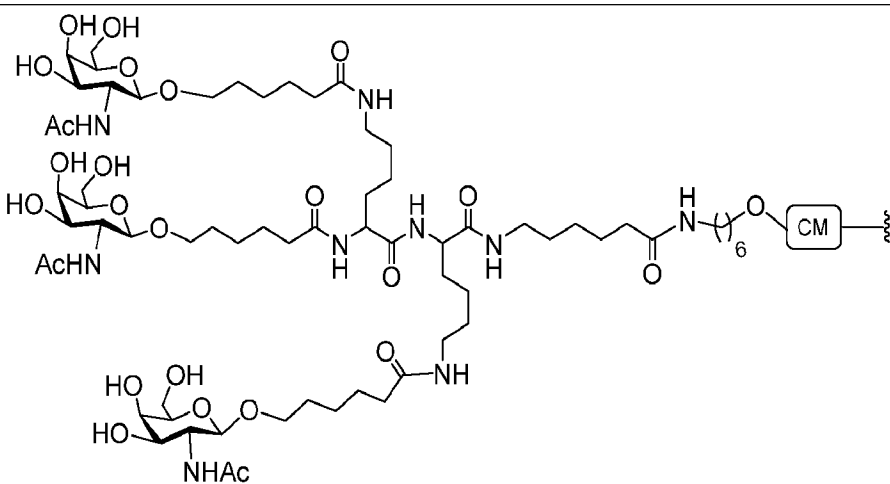
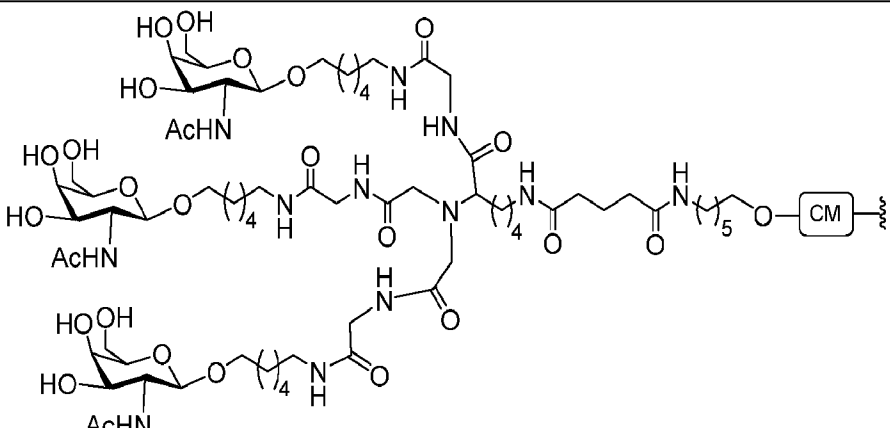
[0431] In certain embodiments, each ligand is N-acetyl galactosamine (GalNAc). In certain embodiments, the cell-targeting moiety comprises one GalNAc ligand. In certain embodiments, the cell-targeting moiety comprises two GalNAc ligands. In certain embodiments, the cell-targeting moiety comprises three GalNAc ligands. In certain embodiments, the cell-targeting moiety comprises a GalNAc ligand cluster. In certain embodiments, the cell-targeting moiety comprises a three GalNAc ligand cluster. In certain embodiments, the cell-targeting moiety is any one of those described in US 9,127,276, the entire contents of which is incorporated herein by reference. In certain embodiments, a conjugate group comprises a cell-targeting moiety selected from any one of the formula set forth in Table 2:

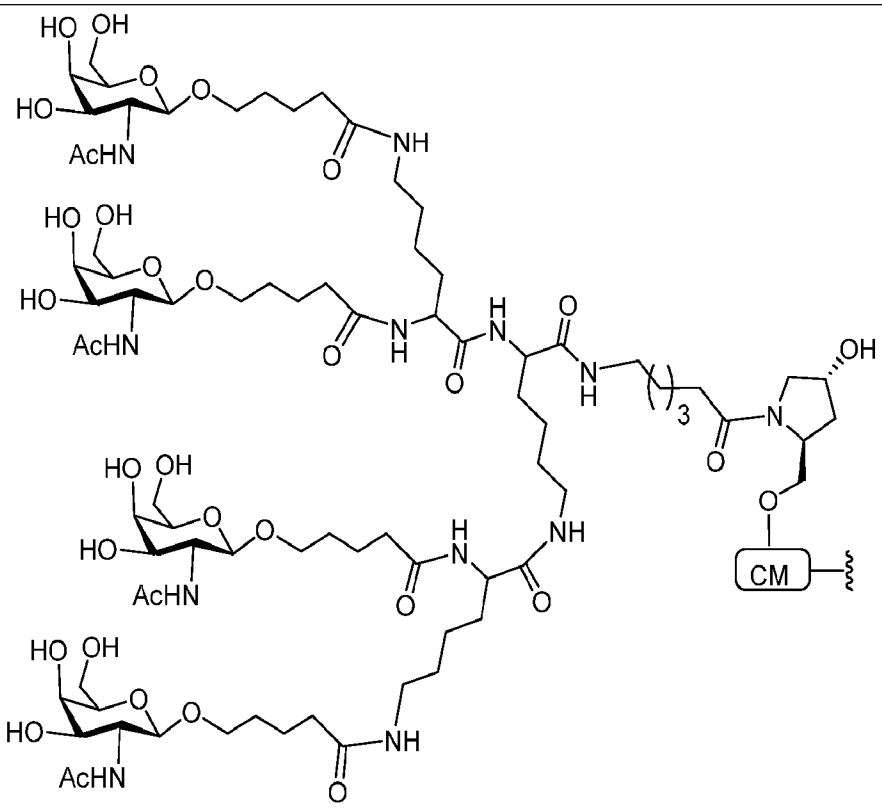
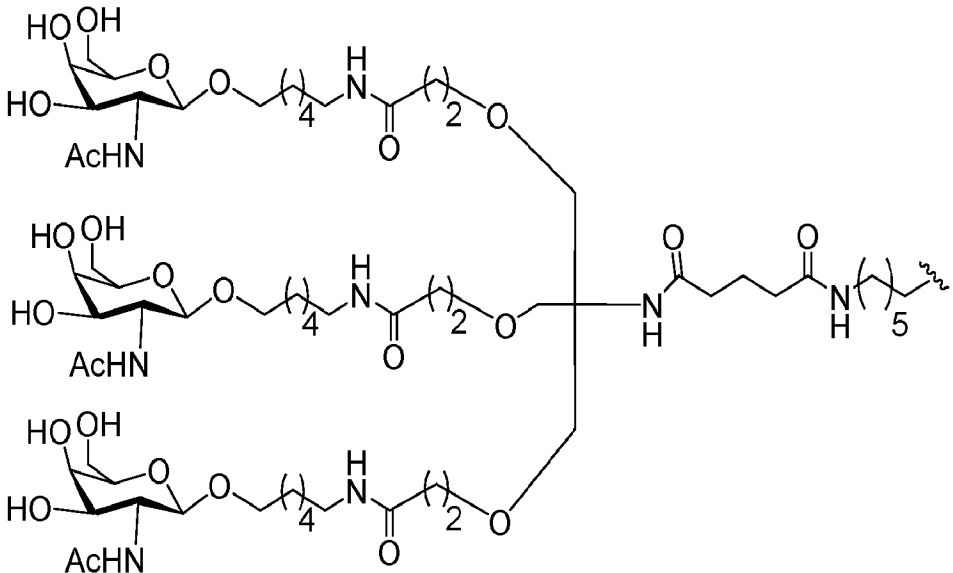
[0432] Table 2: Conjugate groups.

Structure:	Name:
	GalNAc3-7

Structure:	Name:
	GalNAc3-10
	GalNAc3-1
	GalNAc3-3

Structure:	Name:
	GalNAc3-23 (with a cleavable linker moiety)
	GalNAc3-8 (with a cleavable linker moiety)
	GalNAc3-5 (with a cleavable linker moiety)

Structure:	Name:
 The structure shows three galactose units. The top two are linked to a common backbone via their C4 positions. The top galactose has an AcHN group at C2 and is linked to a hexyl chain at C1. The middle galactose has an AcHN group at C2 and is linked to a hexyl chain at C1. The bottom galactose is linked to a hexyl chain at C1 and has an NHAc group at C2. The hexyl chains are connected via amide linkages to a central amide group, which is further connected to a hexyl chain ending in a cleavable linker (CM) moiety.	GalNAc3-13 (with a cleavable linker)
 The structure shows three galactose units. The top two are linked to a common backbone via their C4 positions. The top galactose has an AcHN group at C2 and is linked to a hexyl chain at C1. The middle galactose has an AcHN group at C2 and is linked to a hexyl chain at C1. The bottom galactose is linked to a hexyl chain at C1 and has an NHAc group at C2. The hexyl chains are connected via amide linkages to a central amide group, which is further connected to a hexyl chain ending in a cleavable linker (CM) moiety.	GalNAc3-6 (with a cleavable linker moiety)

Structure:	Name:
	GalNAc4-11 (with a cleavable linker moiety)
	LICA-1

[0433] b. Conjugate Linkers

[0434] In certain embodiments, oligomeric compounds comprise an oligonucleotide and a conjugate group, wherein the conjugate group comprises a conjugate moiety and a conjugate linker. In certain embodiments, the conjugate linker links the conjugate moiety to the oligonucleotide. In certain embodiments, the conjugate linker is a single chemical bond (i.e., the conjugate moiety is attached

directly to an oligonucleotide through a single bond). In certain embodiments, the conjugate linker comprises one or more atoms. In certain embodiments, the conjugate linker comprises a chemical group. In certain embodiments, the conjugate linker comprises a chain structure, such as a hydrocarbyl chain, or an oligomer of repeating units such as ethylene glycol, nucleosides, or amino acid units. In certain embodiments, the oligonucleotide is a modified oligonucleotide.

[0435] In certain embodiments, a conjugate linker comprises one or more groups selected from alkyl, amino, oxo, amide, disulfide, polyethylene glycol, ether, thioether, and hydroxylamino. In certain embodiments, the conjugate linker comprises one or more groups selected from alkyl, amino, oxo, amide and ether groups. In certain embodiments, the conjugate linker comprises one or more groups selected from alkyl and amide groups. In certain embodiments, the conjugate linker comprises one or more groups selected from alkyl and ether groups. In certain embodiments, the conjugate linker comprises at least one phosphorus moiety. In certain embodiments, the conjugate linker comprises at least one phosphate group. In certain embodiments, the conjugate linker includes at least one neutral linking group.

[0436] In certain embodiments, conjugate linkers, including the conjugate linkers described herein, are bifunctional linking moieties, *e.g.*, those known in the art to be useful for attaching conjugate moieties to parent compounds, such as the oligonucleotides provided herein. In general, a bifunctional linking moiety comprises at least two functional groups. One of the functional groups is selected to react with a particular site on a parent compound and the other is selected to react with a peptide extender. Examples of functional groups used in a bifunctional linking moiety include but are not limited to electrophiles for reacting with nucleophilic groups and nucleophiles for reacting with electrophilic groups. In certain embodiments, bifunctional linking moieties comprise one or more groups selected from amino, hydroxyl, carboxylic acid, thiol, alkyl, alkenyl, and alkynyl.

[0437] In certain embodiments, conjugate linkers comprise chemical groups that are formed upon a reaction between a first functional group and a second functional group. In certain embodiments, a modified oligonucleotide is attached to the first functional group during synthesis, and a conjugate moiety is attached to a second functional group during synthesis. Then, the two compounds are mixed under specific conditions to yield the final oligomeric compound. Such reactions that are compatible with both oligonucleotide and peptide chemistry have been previously described and are often called “bioconjugation” reactions. Such reactions include strain promoted azido-alkyne cycloaddition (SPAAC), copper-catalyzed click reaction (CuAAC), active ester conjugation to an amino modified

oligonucleotide, maleimide-thiol Michael addition, ketol/hydroxylamine ligation, the Staudinger ligation, reductive amination, thio ether formation, disulfide formation, reductive alkylation, catalyst-free N-arylation, sulfur fluoride exchange click reaction (SuFEx), and inverse demand Diels Alder reaction. Certain such reactions are described in, e.g., Jbara, et al., "Oligonucleotide Bioconjugation with Bifunctional Palladium Reagents", *Angew. Chem. Int. Ed.* 2021, 60(21):12109-12115; Dong, et al., "Sulfur(VI) Fluoride Exchange (SuFEx): Another Good Reaction for Click Chemistry," *Angew. Chem. Int. Ed.* 2014, 53(36):9430-9448.4; Zhang, et al., "Arylation Chemistry for Bioconjugation," *Angew. Chem. Int. Ed. Engl.* 2019; 58(15): 4810-4839; Walsh, et al., "Site-selective modification strategies in antibody-drug conjugates" *Chem. Soc. Rev.*, 2021, 50: 1305-1353; Tiefenbrunn, et al., "Chemoselective ligation techniques: modern applications of time-honored chemistry", *Biopolymers*, 2010, 94(1):95-106; Drake, et al., *Bioconjug. Chem.* 2014, 25(7):1331-1341; Bode, *Acc. Chem. Res.*, 2017, 50, 9, 2104-2115; J. Magano, B. Bock, et al, *Org. Proc. Res. Dev.* 2014, 18:142-151; Craig S. McKay and M.G. Finn, "Click Chemistry in Complex Mixtures: Bioorthogonal Bioconjugation", *Chemistry & Biology* 2014; Mitchell P. Christy et al., *Org. Lett.* 2020, 22: 2365; Ren et al., *Angew. Chem. Int. Ed. Engl.* 2009, 48, 9658-9662; Rohrbacher, F. et al., *Helv. Chim. Acta.* 2018, 101; Baalman, et al, "A Bioorthogonal Click Chemistry Toolbox for Targeted Synthesis of Branched and Well-Defined Protein-Protein Conjugates", *Angew. Chem. Int. Ed.* 2020 (59): 12885-12893; Lang, et al, "Bioorthogonal Reactions for Labeling Proteins", *J. Am. Chem. Soc.* 2014, 9(1):16-20; Nair, et al., "The Thiol-Michael Addition Click Reaction: A Powerful and Widely Used Tool in Materials Chemistry", *Chem. Mater.* 2013 26(1):724-744; Kalia and Raines, "Hydrolytic Stability of Hydrazones and Oximes", *Angew. Chem. Int. Ed.*, 2008, 47:7523-7526.

[0438] Examples of conjugate linkers include but are not limited to pyrrolidine, 8-amino-3,6-dioxaoctanoic acid (ADO), succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC) and 6-aminohexanoic acid (AHEX or AHA). Other conjugate linkers include but are not limited to substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₂-C₁₀ alkenyl or substituted or unsubstituted C₂-C₁₀ alkynyl, wherein a nonlimiting list of preferred substituent groups includes hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl and alkynyl.

[0439] In certain embodiments, conjugate linkers comprise 1-5 linker-nucleosides. In certain embodiments, conjugate linkers comprise 2-5 linker-nucleosides. In certain embodiments, conjugate linkers comprise exactly 3 linker-nucleosides. In certain embodiments, conjugate linkers comprise

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

[0440] Herein, linker-nucleosides are not considered to be part of the oligonucleotide. Accordingly, in embodiments in which an oligomeric compound comprises an oligonucleotide consisting of a specified number or range of linked nucleosides and/or a specified percent complementarity to a reference nucleic acid and the oligomeric compound also comprises a conjugate linker comprising linker-nucleosides, those linker-nucleosides are not counted toward the length of the oligonucleotide and are not used in determining the percent complementarity of the oligonucleotide for the reference nucleic acid. For example, an oligomeric compound may comprise (1) an oligonucleotide consisting of 18-30 nucleosides and (2) a conjugate linker comprising 1-10 linker-nucleosides that are contiguous with the nucleosides of the oligonucleotide. The total number of contiguous linked nucleosides in such an oligomeric compound is more than 30. Alternatively, an oligomeric compound may comprise an oligonucleotide consisting of 18-30 nucleosides and no conjugate linker. The total number of contiguous linked nucleosides in such an oligomeric compound is no more than 30. Unless otherwise indicated conjugate linkers comprise no more than 10 linker-nucleosides. In certain embodiments, conjugate linkers comprise no more than 5 linker-nucleosides. In certain embodiments, conjugate linkers comprise no more than 3 linker-nucleosides. In certain embodiments, conjugate linkers comprise no more than 2 linker-nucleosides. In certain embodiments, conjugate linkers comprise no more than 1 linker-nucleoside.

[0441] In certain embodiments, it is desirable for a conjugate moiety to be cleaved from the oligonucleotide. For example, in certain circumstances oligomeric compounds comprising a particular conjugate moiety are better taken up by a particular cell type, but once the oligomeric

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

[0442] In certain embodiments, a cleavable bond is selected from among: an amide, an ester, an ether, one or both esters of a phosphodiester, a phosphate ester, a carbamate, or a disulfide. In certain embodiments, a cleavable bond is one or both of the esters of a phosphodiester. In certain embodiments, a cleavable moiety comprises a phosphate or phosphodiester. In certain embodiments, the cleavable moiety is a phosphodiester linkage between an oligonucleotide and a conjugate moiety.

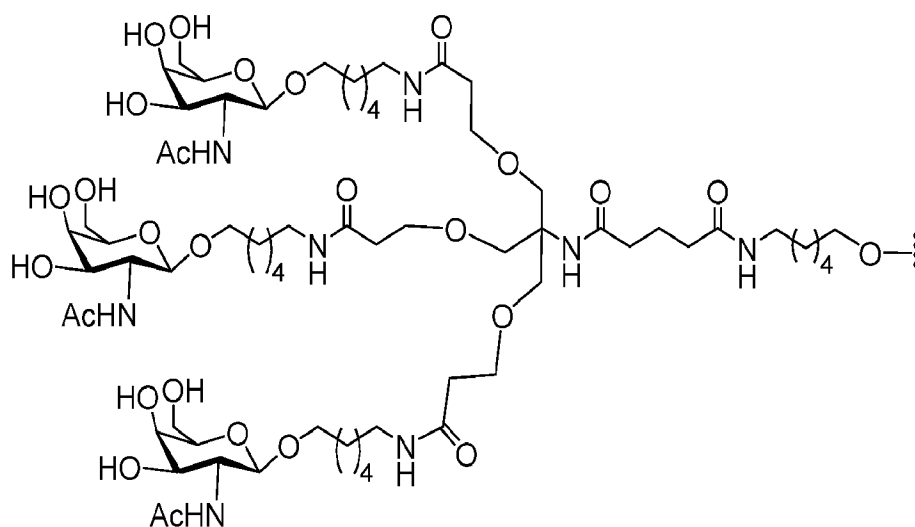
[0443] In certain embodiments, a cleavable moiety comprises or consists of one or more linker-nucleosides. In certain embodiments, the one or more linker-nucleosides are linked to one another and/or to the remainder of the oligomeric compound through cleavable bonds. In certain embodiments, such cleavable bonds are unmodified phosphodiester bonds. In certain embodiments, a cleavable moiety is 2'-deoxy nucleoside that is attached to either the 3' or 5'-terminal nucleoside of an oligonucleotide by a phosphate internucleoside linkage and covalently attached to the remainder of the conjugate linker or conjugate moiety by a phosphate or phosphorothioate linkage. In certain embodiments, the cleavable moiety is 2'-deoxyadenosine.

[0444] In certain embodiments, oligomeric compounds described herein comprise an oligonucleotide linked to a conjugate moiety by a conjugate linker, wherein the oligomeric compound is prepared using Click chemistry known in the art. Compounds have been prepared using Click chemistry wherein alkynyl phosphonate internucleoside linkages on an oligomeric compound attached to a solid support are converted into the 1,2,3-triazolylphosphonate internucleoside linkages and then cleaved from the solid support (Krishna *et al.*, *J. Am. Chem. Soc.* **2012**, *134*(28), 11618-11631), which is incorporated by reference herein in its entirety. Additional conjugate linkers suitable for use in several embodiments are prepared by Click chemistry described in "Click Chemistry for Biotechnology and Materials Science" Ed. Joerg Laham, Wiley 2009, which is incorporated by reference herein in its entirety.

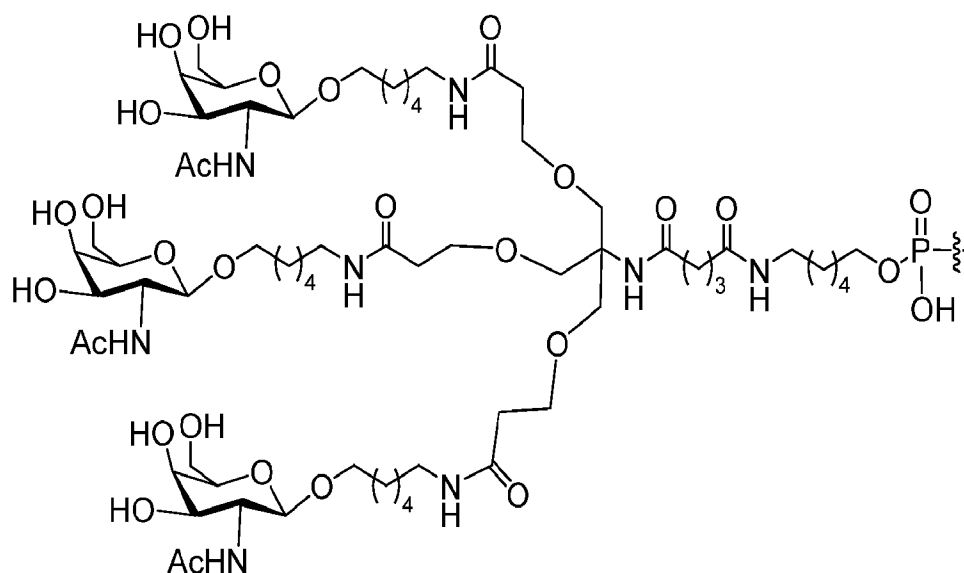
[0445] In certain embodiments, compounds comprise an oligonucleotide, a cell-targeting moiety, and a conjugate linker. In certain embodiments, oligomeric compounds comprise an oligonucleotide, a hepatic asialoglycoprotein receptor (ASGP-R) ligand, and a conjugate linker. In certain embodiments, oligomeric compounds comprise an oligonucleotide, a N-acetyl galactosamine (GalNAc) ligand, and a conjugate linker. In certain embodiments, oligomeric compounds comprise an oligonucleotide, a GalNAc trimer, a branching group, a conjugate linker, and optionally modifications to the GalNAc ligands. In certain embodiments, oligomeric compounds comprise an oligonucleotide, two or more GalNAc ligands, a branching group, a conjugate linker, and optionally modifications to the GalNAc ligands. In certain embodiments, a conjugate linker connects GalNAc ligand to an oligonucleotide.

[0446] In certain embodiments, two or more GalNAc ligands are covalently connected to a conjugate linker, and the conjugate linker is covalently connected to the 3' end of an oligonucleotide. In certain embodiments, a three GalNAc cluster is covalently connected to a conjugate linker, and the conjugate linker is covalently connected to the 3' end of an oligonucleotide. In certain embodiments, two or more GalNAc ligands are covalently connected to a conjugate linker, and the conjugate linker is covalently connected to the 5' end of an oligonucleotide. In certain embodiments, a three GalNAc cluster is covalently connected to a conjugate linker, and the conjugate linker is covalently connected to the 5' end of an oligonucleotide. In certain embodiments, two or more GalNAc ligands are covalently connected to a conjugate linker, and the conjugate linker is covalently connected to an internal position of an oligonucleotide. In certain embodiments, a three GalNAc cluster is covalently connected to a conjugate linker, and the conjugate linker is covalently connected to an internal position of an oligonucleotide. In certain embodiments, an internal position of an oligonucleotide is a 2'-position of a modified sugar moiety of a nucleoside within the internal region of an oligonucleotide that is not the 5' terminal nucleoside or the 3' terminal nucleoside. In certain embodiments, an internal position of an oligonucleotide is a modified internucleoside linkage of the oligonucleotide.

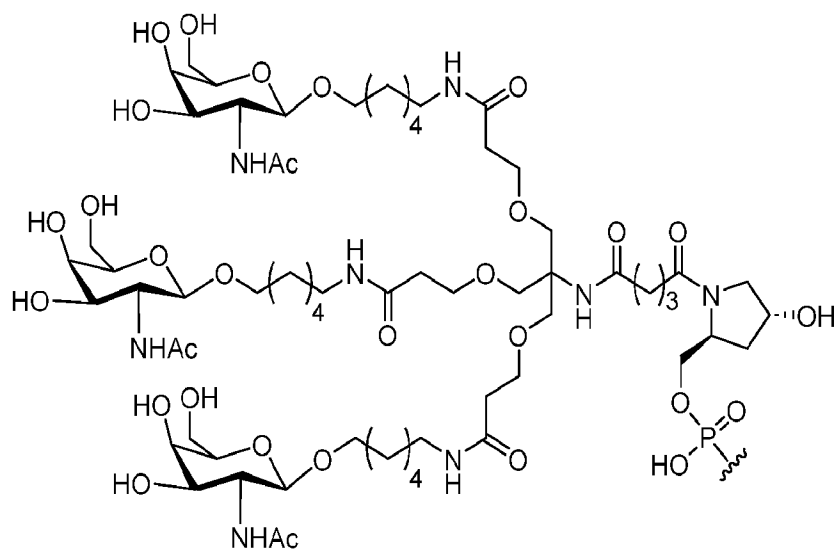
[0447] In certain embodiments, a conjugate group comprises a conjugate trishexylamino (THA)-C6 linker. In certain embodiments, a conjugate group comprises GalNAc is trishexylamino-(THA)-C6 GalNAc₃. In certain embodiments, the trishexylamino-(THA)-C6 GalNAc₃ is attached to the 5'-terminal nucleoside of an oligonucleotide. In certain embodiments, a 5'-Trishexylamino-(THA)-C6 GalNAc₃ conjugate group has the formula:



[0448] In certain embodiments, a modified oligonucleotide is linked to the Trishexylamino-(THA)-C6 GalNAc₃ conjugate by a cleavable moiety. In certain embodiments, the cleavable moiety is a phosphate group. In certain embodiments, the phosphate group is attached to the 5'-oxygen atom of the 5'-nucleoside of the oligonucleotide. In certain embodiments, a 5'-Trishexylamino-(THA)-C6 GalNAc₃ conjugate group containing a cleavable moiety has the formula:



[0449] In certain embodiments, a GalNAc-containing conjugate group is HPPO-GalNAc. In certain embodiments, the HPPO-GalNAc-containing conjugate group is attached to the 3'-terminal nucleoside of an oligonucleotide. In certain embodiments, HPPO-GalNAc conjugate group containing a cleavable moiety has the formula:



[0450] 2. Terminal Groups

[0451] As used herein, “terminal group” means a group of atoms that is covalently linked to a terminus of an oligonucleotide. Examples of a terminal group include, but are not limited to, a capping group, a phosphate moiety, a stabilized phosphate group, and a protecting group, wherein one or more groups is attached to either or both ends of an oligonucleotide. In certain embodiments, one or more terminal groups is attached to either or both ends of an oligonucleotide. In certain embodiments, an oligonucleotide is linked to a terminal group comprising a stabilized 5'-phosphate. In certain embodiments, one or more terminal groups is attached at the 3' and/or 5'-end of the oligonucleotide. In certain embodiments, one or more terminal groups is attached at the 3'-end of the oligonucleotide. In certain embodiments, one or more terminal groups is attached at the 5'-end of the oligonucleotide. In certain embodiments, one or more terminal groups is attached at the 3'-end of the oligonucleotide and one or more terminal groups is attached at the 5'-end of the oligonucleotide. In certain embodiments, a terminal group is attached at the 3' and/or 5'-end of the oligonucleotide. In certain embodiments, a terminal group is attached at the 3'-end of the oligonucleotide. In certain embodiments, a terminal group is attached near the 3'-end of the oligonucleotide. In certain embodiments, a terminal group is attached at the 5'-end of the oligonucleotide. In certain embodiments, a terminal group is attached near the 5'-end of the oligonucleotide. In certain embodiments, a terminal group is attached at the 3'-end of the oligonucleotide and a terminal group is attached at the 5'-end of the oligonucleotide.

[0452] In certain embodiments, a modified oligonucleotide is linked to a terminal group comprising a stabilized phosphate moiety attached to the 5'-end of the oligonucleotide. The stabilized phosphate

moiety results in stabilization of a 5'-phosphate moiety of the 5'-terminal nucleoside of an oligonucleotide, relative to the stability of an unmodified 5'-phosphate of an unmodified nucleoside under biologic conditions. Such stabilization of a 5'-phosphate group includes but is not limited to resistance to removal by phosphatases. Stabilized phosphate moieties, but are not limited to 5'-phosphonates, including, but not limited to 5'-vinylphosphonate, 5'-methylphosphonate, and 5'-cyclopropyl phosphonate. In certain embodiments, the stabilized phosphate moiety is a cyclopropyl phosphonate or an (*E*)-vinyl phosphonate.

[0453] III. COMPOSITIONS

[0454] A. Pharmaceutical Compositions

[0455] In certain embodiments, described herein are compositions comprising or consisting of, or consisting essentially of, an oligomeric agent. In certain embodiments, an oligomeric agent (e.g., a unit dose) contains a modified oligonucleotide (e.g., comprising a nucleobase sequence consisting of 16-30 nucleosides) having a nucleobase sequence complementary to a nucleobase sequence of an equal length target region in an AGT nucleic acid, e.g., a human AGT nucleic acid such as, e.g., SEQ ID NO: 1 or 2. In certain embodiments, the oligomeric agent is any such oligomeric agent described herein and/or containing any such oligonucleotide described herein. In certain embodiments, a composition containing an oligomeric agent is a pharmaceutical composition, e.g., a pharmaceutical formulation. In certain embodiments, the composition contains a pharmaceutically acceptable carrier or excipient. In certain embodiments, the pharmaceutical composition consists of the oligomeric agent and a pharmaceutically acceptable carrier or excipient. In certain embodiments, the oligonucleotide of the oligomeric agent is single-stranded. In certain embodiments, the oligonucleotide of the oligomeric agent is a single-stranded antisense agent, and in certain embodiments is a single-stranded RNase H agent. In certain embodiments, the composition is a pharmaceutical composition consisting of an oligomeric agent consisting of a single-stranded antisense agent, and optionally a conjugate group, and a pharmaceutically acceptable carrier or excipient. In certain embodiments, the nucleobase sequence of the modified oligonucleotide includes at least 12, at least 13, at least 14, at least 15, or at least 16 contiguous nucleobases complementary to an equal length portion of nucleobases 2046-2061 of SEQ ID NO: 1 or nucleobases 14940-14955 of SEQ ID NO: 2. In certain embodiments, the nucleobase sequence of the modified oligonucleotide includes at least 112, at least 13, at least 14, at least 15, or at least 16 contiguous nucleobases of SEQ ID NO: 3, 4 or 5. In certain embodiments of the oligomeric agent-

containing compositions provided herein, the nucleobase sequence of the modified oligonucleotide is SEQ ID NO: 3, 4 or 5. In certain embodiments, the oligomeric agent contains a conjugate group attached to the modified oligonucleotide. In certain embodiments, the conjugate group includes one or more GalNAc moieties (e.g., trisixylamino-(THA)-C6 GalNAc₃). In certain embodiments, the oligomeric agent consists of, or consists essentially of, the modified oligonucleotide and the conjugate group. In certain embodiments, the oligomeric agent comprises or consists of a modified oligonucleotide according to the following chemical notation (5' to 3'):

${}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 4); wherein,

A = an adenine nucleobase,

${}^m\text{C}$ = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

k = a cEt sugar moiety,

d = an unmodified DNA sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

[0456] In certain embodiments, the oligomeric agent is ION904 (represented in certain embodiments by Structure 1), e.g., ION904, and compositions containing ION904, includes any salt (e.g., pharmaceutically acceptable salt) of ION904, e.g., potassium, calcium, magnesium, and sodium salts (see, e.g., Structure 2), ester of ION904, or salts of such esters.

[0457] In certain embodiments, ION904 is represented by the following chemical notation (5' to 3'):

THA-C6-GalNAc₃- ${}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 5);

wherein,

A = an adenine nucleobase,

${}^m\text{C}$ = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

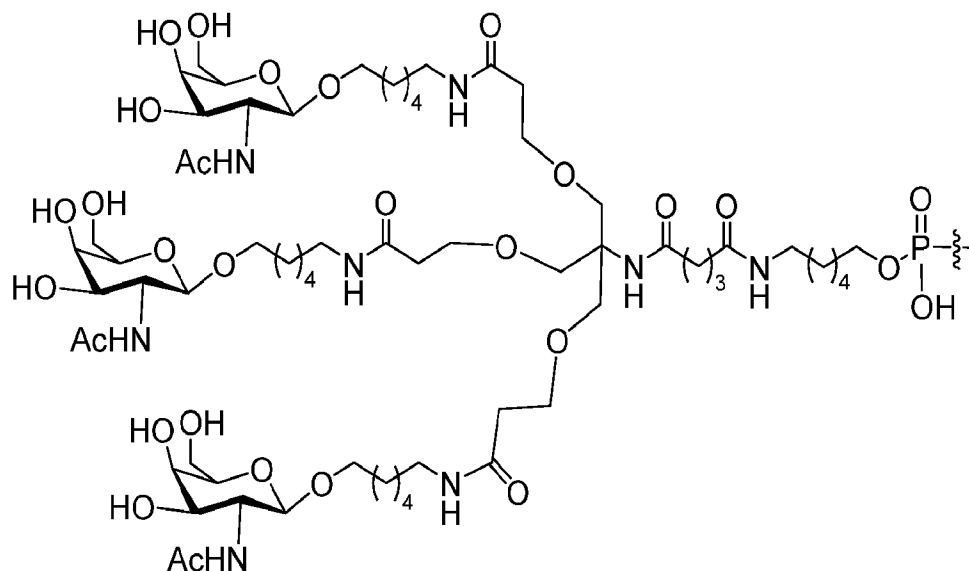
k = a cEt sugar moiety,

d = an unmodified DNA sugar moiety,

s = a phosphorothioate internucleoside linkage,

o = a phosphodiester internucleoside linkage, and

THA-C6-GalNAc₃ =



[0458] In certain embodiments, compositions containing an oligomeric agent that contains a modified oligonucleotide having a nucleobase sequence complementary to a nucleobase sequence of an equal length in an AGT nucleic acid (e.g., a human AGT nucleic acid such as, e.g., SEQ ID NO: 1 or 2), for example, ION904, are used in methods provided herein for reducing the amount of AGT RNA and/or AGT protein in a cell or a subject having or at risk for heart failure, or for treating a subject having or at risk for heart failure. In certain embodiments, a composition containing the oligomeric agent is a pharmaceutical composition. In certain embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or excipient. In certain embodiments, the pharmaceutical composition consists of, or consists essentially of, the oligomeric agent, e.g., ION904, and a pharmaceutically acceptable carrier or excipient. In certain embodiments, the pharmaceutical composition comprises, consists of, or consists essentially of a sterile saline solution and the oligomeric agent, e.g., ION904. In certain embodiments, the pharmaceutical composition comprises, consists of, or consists essentially of a buffered sterile saline solution and the oligomeric agent, e.g., ION904. In certain embodiments, the sterile saline is pharmaceutical grade saline. In certain embodiments, the pharmaceutical composition comprises, consists of, or consists essentially of sterile water and the oligomeric agent, e.g., ION904. In certain embodiments, the sterile water is pharmaceutical grade water. In certain embodiments, the pharmaceutical composition comprises,

consists of, or consists essentially of the oligomeric agent, e.g., ION904, in 2mM phosphate buffered isotonic saline, pH 7.4.

[0459] In certain embodiments, a composition, e.g., pharmaceutical compositions, comprising the oligomeric agent, e.g., ION904, encompass any salt, e.g., any pharmaceutically acceptable salt, of the oligomeric agent, e.g., ION904, esters of the oligomeric agent, e.g., ION904, or salts of such esters. In certain embodiments, pharmaceutical compositions comprising an oligomeric agent, e.g., ION904, 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 salts, e.g., pharmaceutically acceptable salts, of the oligomeric agent, e.g., ION904, prodrugs of the oligomeric agent, e.g., ION904, pharmaceutically acceptable salts of such prodrugs, and other bioequivalents. Suitable pharmaceutically acceptable salts include, but are not limited to, sodium and potassium salts.

[0460] Under certain conditions, an oligomeric agent, e.g., ION904, acts as an acid in a composition. For example, although an oligomeric agent such as ION904 may be drawn or described in protonated (free acid) form, and/or ionized and/or in association with a cation (salt) form, aqueous solutions of the oligomeric agent, e.g., ION904, exist in equilibrium among such forms when in an aqueous composition. For example, a phosphate linkage of ION904 in aqueous solution exists in equilibrium among free acid, anion, and salt forms. Unless otherwise indicated, the term, “ION904,” is intended to include all such forms. Moreover, ION904 has several such linkages, each of which is in equilibrium. Thus, ION904 exists in solution in an ensemble of forms at multiple positions all at equilibrium. The term “ION904” 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 ION904 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.

[0461] In certain embodiments, ION904 is in aqueous solution composition with sodium. In certain embodiments, ION904 is in aqueous solution composition with potassium. In certain embodiments, ION904 is in phosphate-buffered saline (PBS). In certain embodiments, ION904 is in water. In certain embodiments, the pH of the solution is adjusted with NaOH and/or HCl to achieve a desired pH.

[0462] Certain pharmaceutical compositions are formulated based on a mode of delivery.

Pharmaceutical compositions described herein can be administered in a number of different ways, e.g., depending on whether local or systemic treatment is desired and upon the area to be treated. Administration can be, for example, transdermal, epidermal, oral or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal or intramuscular injection or infusion. In certain embodiments, a composition (e.g., pharmaceutical composition) containing an oligomeric agent, e.g., ION904, is administered by subcutaneous injection. In certain embodiments, a composition containing an oligomeric agent, e.g., ION904, is administered by a syringe.

[0463] 2. Doses

[0464] Herein, certain specific doses or quantities are described. For clarity, a dose or quantity of an oligomeric agent, e.g., ION904, in milligrams indicates the mass of the free acid form of the oligomeric agent, e.g., ION904. As described above, in aqueous solution, a free acid is in equilibrium with anionic and salt forms. However, for simplicity of calculating dose or quantity, it is assumed that an oligomeric agent, e.g., ION904, exists as a solvent-free, sodium-acetate free, anhydrous, free acid. For example, where ION904 is in solution comprising sodium (e.g., saline), ION904 may be partially or fully de-protonated and in association with Na⁺ ions, including equilibrium over a combination of multiple different sites throughout the oligomeric compound. However, a mass of proton forms is nevertheless counted toward weight of the dose, and the mass of Na⁺ ions are not counted toward the weight of the dose. Thus, for example, a dose or quantity of 80 mg of ION904 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 ION904.

[0465] In certain embodiments, provided herein are unit doses of an oligomeric agent containing an oligomeric agent (e.g., a unit dose) that contains a modified oligonucleotide (e.g., comprising a nucleobase sequence consisting of 16-30 nucleosides) having a nucleobase sequence complementary to a nucleobase sequence of an equal length target region in an AGT nucleic acid, e.g., a human AGT nucleic acid such as, e.g., SEQ ID NO: 1 or 2. In certain embodiments, the oligomeric agent is any such oligomeric agent described herein containing any such oligonucleotide described herein. Also provided are unit doses of a composition, e.g., pharmaceutical composition, containing such oligomeric agents. In certain embodiments, the composition contains ION904 in any or all forms, including any salt (e.g., pharmaceutically acceptable salt) of ION904, e.g., potassium, calcium,

magnesium, and sodium salts (see, e.g., Structure 2), ester of ION904, or salts of such esters. In certain embodiments, the composition containing an oligomeric agent, e.g., ION904, that contains a oligomeric agent (e.g., a modified oligonucleotide comprising a nucleobase sequence consisting of 16-30 nucleosides) having a nucleobase sequence complementary to a nucleobase sequence of an equal length in an AGT nucleic acid, e.g., a human AGT nucleic acid such as, e.g., SEQ ID NO: 1 or 2, does not contain any other any RAAS inhibitor, e.g., an ACEi, ARB, ARNI, renin inhibitor or MRA. In certain embodiments, the composition does not contain a neprilysin inhibitor. In certain embodiments, the composition does not contain any GDMT for heart failure. In certain embodiments, the composition does not contain any other active agent.

[0466] In certain embodiments, a composition, e.g., pharmaceutical composition, containing an oligomeric agent (e.g., a unit dose) that contains a modified oligonucleotide (e.g., comprising a nucleobase sequence consisting of 16-30 nucleosides) having a nucleobase sequence complementary to a nucleobase sequence of an equal length in an AGT nucleic acid, e.g., a human AGT nucleic acid such as, e.g., SEQ ID NO: 1 or 2, contains another active agent. In certain embodiments, the composition contains a RAAS inhibitor. In certain embodiments, the RAAS inhibitor is an ACEi, ARB, ARNi, renin inhibitor, MRA, or combination of any one or more such RAAS inhibitors. In certain embodiments, the composition contains a neprilysin inhibitor, e.g., sacubitril. In certain embodiments, the composition contains any GDMT for heart failure, e.g., HFrEF. In certain embodiments, the composition contains a GDMT drug (e.g., ACEi, ARB, ARNi, or MRA) at a dose that is less than the Guideline-recommended initial dose, less than the Guideline-recommended target dose. In certain embodiments, the composition contains a GDMT drug at a dose that is less than about 70%, less than about 60%, less than about 50%, or less than about 40% of the Guideline-recommended target dose.

[0467] Guideline-directed medical therapy (GDMT) definitions were developed by the American (American College of Cardiology (ACC), American Heart Association, (AHA) and Heart Failure Society of America (HFSA)) and European (European Society of Cardiology; ESC) societies based on the results of multiple landmark randomized controlled clinical trials and, using this evidence-based approach, provided guideline recommendations for the management of heart failure, including HFrEF, HFmrEF and HFpEF. A recent statement of GDMT for heart failure developed by the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines describes four classes of drugs (1) RAASi (ARNi as a first line, though ACEi and/or

ARB can be used if cannot tolerate ARNi), (2) MRA, (3) β -blockers and (4) SGLT2 inhibitors (Heidenreich et al (2022) *Circulation* 145(18):e895-e1032, 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines) recommended for use in treating heart failure (e.g., HFrEF). The professional society guidelines advise against use of ACEi in patients with a history of angioedema and advise use of ARB in these cases, although some very rare cases of angioedema have been reported with ARB use in landmark trials. ACEi use is also associated with chronic cough in some patients, and society guidelines recommend use of ARB in these cases. The professional societies also direct that ACEi, ARB, ARNi and MRA should be administered with caution to patients with low systemic blood pressures, renal insufficiency or elevated serum potassium (> 5.0 mEq/L), and, if maximal doses are not tolerated, intermediate doses should be tried. Table 14 of the 2022 GDMT (an excerpt of which is shown in Table 3, provides initial and target doses of ACEi, ARB, ARNi, MRA, β -blockers and SGLT2 inhibitor drugs used for HFrEF.

[0468] Table 3: Guideline recommended doses of drugs used for treating HFrEF.

Drug	ESC Target Dose	ACC/AHA/HFSA Target Dose	< 50% Target Dose (mg daily)
Captopril	50 mg 3 times daily	50 mg 3 times daily	<75 (25 mg 3 times daily)
Enalapril	10-20 mg twice daily	10-20 mg twice daily	<10 (5 mg twice daily)
Fosinopril		40 mg once daily	<20 mg daily
Lisinopril	20-35 mg once daily	20-40 mg once daily	<10 mg daily
Perindopril		8-16 mg once daily	<4 mg daily
Quinapril		20 mg twice daily	<20 (10 mg twice daily)
Ramipril	5 mg twice daily	10 mg once daily	<5 mg daily (2.5 mg twice daily)
Trandolipril	4 mg once daily	4 mg once daily	<2 mg daily

Drug	ESC Target Dose	ACC/AHA/HFSA Target Dose	< 50% Target Dose (mg daily)
Candesartan	32 mg once daily	32 mg once daily	<16 mg daily
Losartan	150 mg once daily	50-150 mg once daily	<25 mg daily
Valsartan	160 mg twice daily	160 mg twice daily	<160 mg (80 mg twice daily)
Sacubitril-Valsartan	97 mg sacubitril and 103 mg valsartan twice daily	97 mg sacubitril and 103 mg valsartan twice daily	<200 mg (24 mg sacubitril and 26 mg valsartan twice daily)
Spirolactone	50 mg once daily	25-50 mg once daily	<12.5 mg daily
Eplerenone	50 mg once daily	50 mg once daily	<25 mg daily
Bisoprolol		10 mg once daily	
Carvedilol		25-50 mg twice daily	
Carvedilol CR		80 mg once daily	
Metoprolol succinate extended release (metoprolol CR/XL)		200 mg once daily	
Dapagliflozin		10 mg once daily	
Empagliflozin		10 mg once daily	

[0469] In certain embodiments of a unit dose of a composition provided herein, the quantity of the oligomeric agent, e.g., ION904, in the unit dose is effective to, when administered to a cell or

subject, decrease the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 70%, at least 75%, at least 80%, or at least 85% compared to the amount or level of AGT RNA and/or AGT protein prior to any administration of the oligomeric agent (e.g., the baseline level or amount, or pre-administration level, of AGT RNA and/or AGT protein in the cell or subject). In certain embodiments, the maximum decrease in the amount or level of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT protein) is less than 95%, or less than 94%, or less than 93%, or less than 92%, or less than 91%, or less than 90% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, the amount or level of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT protein) decreases no more than 85%, or no more than 86%, or no more than 87%, or no more than 88%, or no more than 89%, or no more than 90%, or no more than 91%, or no more than 92%, or no more than 93%, or no more than 94%, or no more than 95%, compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, the quantity of the oligomeric agent, e.g., ION904, in the unit dose is effective to, when administered to a cell or subject, decrease the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, the quantity of the oligomeric agent, e.g., ION904, in the unit dose is effective to, when administered to a cell or subject, decrease the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 70%, at least 75%, at least 80% or at least 85% and less than 94% compared to the amount or level of AGT RNA and/or AGT protein prior to any administration of the oligomeric agent (i.e., the baseline level or amount of AGT RNA and/or AGT protein in a cell or subject). In certain embodiments, the quantity of the oligomeric agent, e.g., ION904, in the unit dose is effective to, when administered to a cell or subject, decrease the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT

RNA and/or AGT protein) by at least 70%, at least 75%, at least 80% or at least 85% and less than 93% compared to the amount or level of AGT RNA and/or AGT protein prior to any administration of the oligomeric agent (i.e., the baseline level or amount of AGT RNA and/or AGT protein in a cell or subject). In certain embodiments, the quantity of the oligomeric agent, e.g., ION904, in the unit dose is effective to, when administered to a cell or subject, decrease the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 70%, at least 75%, at least 80% or at least 85% and less than 92% compared to the amount or level of AGT RNA and/or AGT protein prior to any administration of the oligomeric agent (i.e., the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject). In certain embodiments, the quantity of the oligomeric agent, e.g., ION904, in the unit dose is effective to, when administered to a cell or subject, decrease the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 70%, at least 75%, at least 80% or at least 85% and less than 91% compared to the amount or level of AGT RNA and/or AGT protein prior to any administration of the oligomeric agent (i.e., the baseline level or amount of AGT RNA and/or AGT protein in a cell or subject). In certain embodiments, the quantity of the oligomeric agent, e.g., ION904, in the unit dose is effective to, when administered to a cell or subject, decrease the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 70%, at least 75%, at least 80% or at least 85% and less than 90% compared to the amount or level of AGT RNA and/or AGT protein prior to any administration of the oligomeric agent (i.e., the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject). In certain embodiments, the quantity of the oligomeric agent, e.g., ION904, in the unit dose is effective to, when administered to a cell or subject, decrease the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 70%, at least 75%, at least 80% or at least 85% and less than 89% compared to the amount or level of AGT RNA and/or AGT protein prior to any administration of the oligomeric agent (i.e., the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject).

[0470] In certain embodiments, the quantity of the oligomeric agent, e.g., ION904, in the unit dose is effective to, when administered to a cell or subject, decrease the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 70% but less than 95%, less than 94%, less than 93%, less than 92%, less than 91%, less than 90%, less than 89%, less than 88%, or less than 85% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, the quantity of the oligomeric agent, e.g., ION904, in the unit dose is effective to, when administered to a cell or subject, decrease the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 75% but less than 95%, less than 94%, less than 93%, less than 92%, less than 91%, less than 90%, less than 89%, less than 88%, or less than 85% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, the quantity of the oligomeric agent, e.g., ION904, in the unit dose is effective to, when administered to a cell or subject, decrease the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 80% but less than 95%, less than 94%, less than 93%, less than 92%, less than 91%, less than 90%, less than 89%, less than 88%, or less than 85% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, the quantity of the oligomeric agent, e.g., ION904, in the unit dose is effective to, when administered to a cell or subject, decrease the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 85% but less than 95%, less than 94%, less than 93%, less than 92%, less than 91%, less than 90%, or less than 89% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, the quantity of the oligomeric agent, e.g., ION904, in the unit dose is effective to, when administered to a cell or subject, decrease the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by 70%-90%, 70%-89%, 70%-88%, 70%-87%, 70%-86%, 70%-85%, 70%-84%, 70%-83%, 70%-82%, 70%-81%, 70%-80%, 75%-90%, 75%-89%, 75%-88%, 75%-87%, 75%-86%, 75%-85%, 75%-84%, 75%-83%, 75%-82%, 75%-81%, 75%-80%,

76%-90%, 76%-89%, 76%-88%, 76%-87%, 76%-86%, 76%-85%, 76%-84%, 76%-83%, 76%-82%, 76%-81%, 76%-80%, 77%-90%, 77%-89%, 77%-88%, 77%-87%, 77%-86%, 77%-85%, 77%-84%, 77%-83%, 77%-82%, 77%-81%, 77%-80%, 78%-90%, 78%-89%, 78%-88%, 78%-87%, 78%-86%, 78%-85%, 78%-84%, 78%-83%, 78%-82%, 78%-81%, 78%-80%, 79%-90%, 79%-89%, 79%-88%, 79%-87%, 79%-86%, 79%-85%, 79%-84%, 79%-83%, 79%-82%, 79%-81%, 79%-80%, 80%-90%, 80%-89%, 80%-88%, 80%-87%, 80%-86%, 80%-85%, 80%-84%, 80%-83%, 80%-82%, 81%-90%, 81%-89%, 81%-88%, 81%-87%, 81%-86%, 81%-85%, 81%-84%, 81%-83%, 81%-82%, 82%-90%, 82%-89%, 82%-88%, 82%-87%, 82%-86%, 82%-85%, 82%-84%, 82%-83%, 83%-90%, 83%-89%, 83%-88%, 83%-87%, 83%-86%, 83%-85%, 83%-84%, 84%-90%, 84%-89%, 84%-88%, 84%-87%, 84%-86%, 84%-85%, 85%-90%, 85%-89%, 85%-88%, 85%-87%, 85%-86%, 86%-90%, 86%-89%, 86%-88%, 86%-87%, 87%-90%, 87%-89%, 87%-88%, 88%-90%, or 88%-89% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject.

[0471] In certain embodiments of the unit doses of a composition provided herein, the quantity of the oligomeric agent, e.g., ION904, in the unit dose is effective to treat, and/or ameliorate one or more symptoms of, heart failure, such as HFrEF, HFmrEF or HFpEF, but does not significantly alter (e.g., decrease) systemic blood pressure (e.g., systolic blood or diastolic blood pressure) in a subject having, or at risk for, heart failure, including, e.g., a subject having, or at risk for heart failure who has hypotension (low blood pressure) or normal blood pressure (normotension). In certain embodiments, a significant alteration in systolic or diastolic blood pressure is a greater than about 10 mm Hg change in blood pressure, or a greater than about 11 mm Hg change in blood pressure, or a greater than about 12 mm Hg change in blood pressure, or a greater than about 13 mm Hg change in blood pressure, or a greater than about 14 mm Hg change in blood pressure, or a greater than about 15 mm Hg change in blood pressure. In certain embodiments, normal systolic blood pressure is within the range of about 90 mm Hg or 100 mm Hg to about 120 mm Hg or 125 mm Hg, and normal diastolic blood pressure is within the range of about 60 mm Hg and about 80 mm Hg. In certain embodiments, low systolic blood pressure is less than about 90 mm Hg and low diastolic blood pressure is less than about 60 mm Hg. In certain embodiments, elevated systolic blood pressure is about 125 mm Hg to about 129 mm Hg and high systolic blood pressure (i.e., hypertension) is about 130 mm Hg or higher. In certain embodiments, the quantity of oligomeric agent, e.g., ION904, in the unit dose is effective in treating, and/or ameliorating one or more symptoms of, HFrEF, but does not significantly alter (e.g., decrease) systemic blood pressure (e.g., systolic blood or diastolic blood

pressure) in a subject having, or at risk for, HFrEF, including, e.g., a subject having, or at risk for heart failure who has hypotension or normal blood pressure.

[0472] In certain embodiments, the quantity of oligomeric agent, e.g., ION904, in the unit dose is effective in treating, and/or ameliorating one or more symptoms of, heart failure, such as HFrEF, HFmrEF or HFpEF, but does not significantly alter (e.g., increase) potassium levels (e.g., blood, serum or plasma potassium levels) in a subject having, or at risk for heart failure (such as HFrEF, HFmrEF or HFpEF), including, for example, a subject having, or at risk for, heart failure who has hyperkalemia, renal dysfunction, or renal insufficiency, acute kidney injury (AKI), or chronic kidney disease (CKD). In certain embodiments, hyperkalemia is a high potassium level (e.g., serum potassium level) of greater than about 5.0 mEq/L or about 5.5 mEq/L, elevated serum potassium level is greater than about 4.0 mEq/L, and normal potassium levels are within the range of about 3.5 mEq/L to about 5.0 mEq/L. In certain embodiments, renal insufficiency is associated with an eGFR of less than about 90 ml/min/1.73 m² or about 100 ml/min/1.73 m² (or eGFR between 30 and 90 ml/min/1.73 m², ≤ 40 ml/min/1.73 m², ≤ 35 ml/min/1.73 m², or ≤ 30 ml/min/1.73 m²), stage 2 kidney disease is associated with an eGFR within the range of about 60 ml/min/1.73 m² to about 89 ml/min/1.73 m², stage 3 kidney disease is associated with an eGFR within the range of about 30 ml/min/1.73 m² to about 59 ml/min/1.73 m², stage 4 kidney disease is associated with an eGFR within the range of about 15 ml/min/1.73 m² to about 29 ml/min/1.73 m², and stage 5 kidney disease (kidney failure) is associated with an eGFR of less than about 15 ml/min/1.73 m². In certain embodiments, the quantity of oligomeric agent e.g., ION904, in the unit dose is effective in treating, and/or ameliorating one or more symptoms of, HFrEF, but does not significantly alter (e.g., increase) potassium levels (e.g., blood, serum or plasma potassium levels) in a subject having, or at risk for HFrEF, including, e.g., a subject having, or at risk for HFrEF who has renal insufficiency.

[0473] In certain embodiments, the amount of oligomeric agent e.g., ION904, in the unit dose is effective in treating, and/or ameliorating one or more symptoms of, heart failure, such as HFrEF, HFmrEF or HFpEF, but does not significantly alter bradykinin homeostasis and/or increase bradykinin levels (e.g., blood, serum, or plasma bradykinin levels) in a subject having, or at risk for heart failure (such as HFrEF, HFmrEF or HFpEF), including, for example, a subject having, or at risk for heart failure who has pulmonary disease or angioedema. In certain embodiments, the quantity of oligomeric agent e.g., ION904, in the unit dose is effective in treating, and/or ameliorating one or more symptoms of, HFrEF, but does not significantly alter bradykinin

homeostasis and/or increase bradykinin levels (e.g., blood, serum, or plasma bradykinin levels) in a subject having, or at risk for HFrEF, including, e.g., a subject having, or at risk for heart failure who has pulmonary disease or angioedema. Bradykinin homeostasis is maintained through balanced levels of bradykinin formation and degradation. Alteration of bradykinin homeostasis can result in relatively elevated bradykinin levels which leads to increased vascular permeability. Increased vascular permeability allows for increased fluid leakage from blood vessels into tissues which can result in angioedema (e.g., non-allergic angioedema). Additionally, bradykinin can trigger bronchoconstriction in the respiratory tract, which may lead to cough development.

[0474] In certain embodiments, the quantity of oligomeric agent e.g., ION904, in the unit dose improves cardiac function, reduces cardiac dilation, reduces cardiac fibrosis, reverses or attenuates cardiac remodeling, and/or increases LVEF in a subject having, or at risk for, heart failure (such as HFrEF, HFmrEF or HFpEF). In certain embodiments the quantity of oligomeric agent e.g., ION904, in the unit dose improves cardiac function, reduces cardiac dilation, reduces cardiac fibrosis, reverses or attenuates cardiac remodeling, and/or increases LVEF in a subject having, or at risk for, HFrEF. In certain embodiments, the quantity of oligomeric agent e.g., ION904, in the unit dose improves improve left ventricular end diastolic volume (LVEDV), improves left ventricle (LV) strain, improves 6-minute walk test, and/or improves quality of life as assessed by patient reported outcomes of a subject having, or at risk for, heart failure. In certain embodiments, the quantity of oligomeric agent e.g., ION904, in the unit dose improves left ventricular indexed end systolic volume (ESVi) or left ventricular end systolic volume (LVESV) of a subject having, or at risk for, heart failure (such as HFrEF, HFmrEF, HFimpEF or HFpEF). In certain embodiments, the quantity of oligomeric agent e.g., ION904, in the unit dose improves ESVi or LVESV of a subject having, or at risk for, HFrEF. In certain embodiments, the quantity of oligomeric agent e.g., ION904, in the unit dose decreases the level of N-terminal prohormone B-type natriuretic peptide (NT-proBNP), B-type natriuretic peptide (BNP), high-sensitive cardiac troponin T (hs-cTnT), and/or cardiac troponin T (cTnT) in plasma of a subject having, or at risk for, heart failure (such as HFrEF, HFmrEF or HFpEF) compared to the level prior to administration of the unit dose, or to the baseline level in a subject before any administration of the oligomeric agent, e.g., ION904. In certain embodiments, the quantity of oligomeric agent e.g., ION904, in the unit dose decreases the level NT-proBNP, BNP, high-sensitive cardiac troponin T (hs-cTnT) and/or cTnT in plasma of a subject having, or at risk

for, HFrEF compared to the level prior to administration of the unit dose, or to the baseline level in a subject before any administration of the oligomeric agent, e.g., ION904.

[0475] In certain embodiments of the unit doses of a composition provided herein, the unit dose is administered as a loading dose. In certain embodiments, administration of one or more loading dose is effective in achieving a desired condition in a subject, for example, a desired initial concentration of oligomeric agent, e.g., ION904. In certain embodiments, administration of the loading dose(s) is/are effective in decreasing the amount or level of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) compared to the amount or level of AGT RNA and/or AGT protein prior to administration of the loading dose of the oligomeric agent (e.g., the baseline or pre-administration level of AGT). In certain embodiments, a unit dose, e.g., a loading dose, is effective to decrease the amount or level of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by 20%-95%, 20%-90%, 20%-89%, 20%-88%, 20%-87%, 20%-86%, 20%-85%, 20%-84%, 20%-83%, 20%-82%, 20%-81%, 20%-80%, 20%-79%, 20%-78%, 20%-77%, 20%-76%, 20%-75%, 20%-74%, 20%-73%, 20%-72%, 20%-71%, 20%-70%, 20%-65%, 20%-60%, 20%-55%, 20%-50%, 50%-95%, 50%-90%, 50%-89%, 50%-88%, 50%-87%, 50%-86%, 50%-85%, 50%-84%, 50%-83%, 50%-82%, 50%-81%, 50%-80%, 50%-79%, 50%-78%, 50%-77%, 50%-76%, 50%-75%, 50%-74%, 50%-73%, 50%-72%, 50%-71%, 50%-70%, 50%-65%, 50%-60%, 60%-95%, 60%-90%, 60%-89%, 60%-88%, 60%-87%, 60%-86%, 60%-85%, 60%-84%, 60%-83%, 60%-82%, 60%-81%, 60%-80%, 60%-79%, 60%-78%, 60%-77%, 60%-76%, 60%-75%, 60%-74%, 60%-73%, 60%-72%, 60%-71%, 60%-70%, 60%-65%, 70%-95%, 70%-90%, 70%-89%, 70%-88%, 70%-87%, 70%-86%, 70%-85%, 70%-84%, 70%-83%, 70%-82%, 70%-81%, 70%-80%, 80%-95%, 80%-90%, 80%-89%, 80%-88%, 80%-87%, 80%-86%, 80%-85%, 90%-95%, 90%-94%, 90%-93%, or 90%-92% compared to the amount or level of AGT RNA and/or AGT protein prior to administration of the loading dose of the oligomeric agent. In certain embodiments, administration of the loading dose(s) is more effective to decrease the amount or level of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) than administration of a maintenance dose is to decrease the amount or level of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA

and/or AGT protein). In certain embodiments, administration of a loading dose(s) is less effective in decreasing the amount or level of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) than administration of a maintenance dose is to decrease the amount or level of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein). In certain embodiments, the quantity of the oligomeric agent, e.g., ION904, in a unit dose that is a loading dose is greater than the quantity of the oligomeric agent, e.g., ION904, in a unit dose that is a maintenance dose. In certain embodiments, the quantity of the oligomeric agent, e.g., ION904, in a unit dose that is a loading dose is less than the quantity of the oligomeric agent, e.g., ION904, in a unit dose that is a maintenance dose.

[0476] In certain embodiments of the unit doses of a composition provided herein, the unit dose is administered as a maintenance dose. In certain embodiments, administration of the maintenance dose is effective in maintaining a desired condition in a subject that results from administration of the loading dose. In certain embodiments, administration of the maintenance dose is effective in maintaining an amount or level of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) that is less than the amount or level of AGT RNA and/or AGT protein prior to administration of the loading dose of the oligomeric agent (e.g., the baseline or pre-administration level of AGT). In certain embodiments, administration of the maintenance dose is effective in maintaining an amount or level of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) that is about the same as the amount or level of AGT RNA and/or AGT protein after administration of the loading dose, that is less than the amount or level of AGT RNA and/or AGT protein after administration of the loading dose, or that is more than the amount or level of AGT RNA and/or AGT protein after administration of the loading dose but less than the amount or level of AGT RNA and/or AGT protein prior to administration of the loading dose of the oligomeric agent (e.g., the baseline or pre-administration level of AGT). In certain embodiments, the quantity of the oligomeric agent, e.g., ION904, in a unit dose that is a maintenance dose is greater than the quantity of the oligomeric agent, e.g., ION904, in a unit dose that is a loading dose. In certain embodiments, the quantity of the oligomeric agent, e.g., ION904, in a unit does that is a

maintenance dose is less than the quantity of the oligomeric agent, e.g., ION904, in a unit dose that is a loading dose.

[0477] In certain embodiments of the unit doses of a composition provided herein, the quantity of the oligomeric agent, e.g., ION904, in a unit dose is within the range of about 15 mg to about 200 mg, about 20 mg to about 200 mg, about 40 mg to about 150 mg, about 60 mg to about 150 mg, about 60 mg to about 140 mg, about 65 mg to about 140 mg, about 70 mg to about 140 mg, about 75 mg to about 120 mg, about 80 mg to about 120 mg, about 85 mg to about 120 mg, about 90 mg to about 120 mg, about 95 mg to about 120 mg, about 100 mg to about 120 mg, about 60 mg to about 110 mg, about 65 mg to about 110 mg, about 70 mg to about 110 mg, about 75 mg to about 110 mg, about 80 mg to about 110 mg, about 85 mg to about 110 mg, about 90 mg to about 110 mg, about 95 mg to about 110 mg, about 100 mg to about 110 mg, about 60 mg to about 100 mg, about 65 mg to about 100 mg, about 70 mg to about 100 mg, about 75 mg to about 100 mg, about 80 mg to about 100 mg, about 85 mg to about 100 mg, about 90 mg to about 100 mg, or about 95 mg to about 100 mg.

[0478] In certain embodiments of the unit doses of a composition provided herein, the quantity of the oligomeric agent, e.g., ION904, in a unit dose is within the range of about 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.

[0479] In certain embodiments of the unit doses of a composition provided herein, the quantity of the oligomeric agent, e.g., ION904, in a unit dose is at least about 20 mg and less than 200 mg, at least about 20 mg and less than 195 mg, at least about 20 mg and less than 190 mg, at least about 20 mg and less than 185 mg, at least about 20 mg and less than 180 mg, at least about 20 mg and less than 175 mg, at least about 20 mg and less than 170 mg, at least about 20 mg and less than 165 mg, at least about 20 mg and less than 160 mg, at least about 20 mg and less than 155 mg, at least about 20 mg and less than 150 mg, at least about 20 mg and less than 145 mg, at least about 20 mg and less than 140 mg, at least about 20 mg and less than 135 mg, at least about 20 mg and less than 130 mg, at least about 20 mg and less than 125 mg, at least about 20 mg and less than 120 mg, at least about 20 mg and less than 115 mg, at least about 20 mg and less than 110 mg, at least about 20 mg and less than 105 mg, at least about 20 mg and less than 100 mg, at least about 20 mg and less than 95 mg, at least about 20 mg and less than 90 mg, at least about 20 mg and less than 85 mg, at least about 20 mg and less than 80 mg, at least about 20 mg and less than 75 mg, at least about 20 mg and less than 70 mg, at least about 20 mg and less than 65 mg, at least about 20 mg and less than 60 mg, at least about 20 mg and less than 55 mg, at least about 20 mg and less than 50 mg, at least about 20 mg and less than 45 mg, at least about 20 mg and less than 40 mg, at least about 20 mg and less than 35 mg, or at least about 20 mg and less than 30 mg.

[0480] In certain embodiments of the unit doses of a composition provided herein, the quantity of the oligomeric agent, e.g., ION904, in a unit dose is at least about 20 mg and less than about 200 mg, at least about 20 mg and less than about 195 mg, at least about 20 mg and less than about 190 mg, at least about 20 mg and less than about 185 mg, at least about 20 mg and less than about 180 mg, at least about 20 mg and less than about 175 mg, at least about 20 mg and less than about 170 mg, at least about 20 mg and less than about 165 mg, at least about 20 mg and less than about 160 mg, at least about 20 mg and less than about 155 mg, at least about 20 mg and less than about 150 mg, at least about 20 mg and less than about 145 mg, at least about 20 mg and less than about 140 mg, at least about 20 mg and less than about 135 mg, at least about 20 mg and less than about 130 mg, at least about 20 mg and less than about 125 mg, at least about 20 mg and less than about 120 mg, at least about 20 mg and less than about 115 mg, at least about 20 mg and less than about 110 mg, at least about 20 mg and less than about 105 mg, at least about 20 mg and less than about 100 mg, at least about 20 mg and less than about 95 mg, at least about 20 mg and less than about 90 mg, at least about 20 mg and less than about 85 mg, at least about 20 mg and less than about 80 mg, at least about 20 mg and less than about 75 mg, at least about 20 mg and less than about 70 mg, at least about 20 mg and less than about 65 mg, at least about 20 mg and less than about 60 mg, at least about 20 mg and less than about 55 mg, at least about 20 mg and less than about 50 mg, at least about 20 mg and less than about 45 mg, at least about 20 mg and less than about 40 mg, at least about 20 mg and less than about 35 mg, or at least about 20 mg and less than about 30 mg.

[0481] In certain embodiments of the unit doses of a composition provided herein, the quantity of the oligomeric agent, e.g., ION904, in a unit dose is about 15 mg, about 20 mg, about 30 mg, about 40 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, or about 150 mg. In certain embodiments of the unit doses of a composition provided herein, the quantity of the oligomeric agent, e.g., ION904, in the unit dose is 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, or about 110 mg.

[0482] In certain embodiments of the unit doses of a composition provided herein, the quantity of the oligomeric agent, e.g., ION904, in a unit dose is 15 mg, 20 mg, 30 mg, 40 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, or 150 mg. In certain embodiments of the unit doses of a composition provided herein, the quantity of the oligomeric agent, e.g., ION904, in the unit dose is 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, or 110 mg.

[0483] In certain embodiments of the unit doses of a composition provided herein, the quantity of the oligomeric agent, e.g., ION904, in a unit dose is within the range of about 60 mg to about 110 mg, about 75 mg to about 110 mg, about 85 mg to about 110 mg, about 90 mg to about 110 mg, about 95 mg to about 110 mg, about 100 mg to about 110 mg, about 80 mg to about 100 mg, about 85 mg to about 100 mg, or about 90 mg to about 100 mg. In certain embodiments of the unit doses of a composition provided herein, the quantity of the oligomeric agent, e.g., ION904, in the unit dose is 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, or about 120 mg. In certain embodiments of the unit doses of a composition provided herein, the quantity of the oligomeric agent, e.g., ION904, in the unit dose is 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 105 mg, 110 mg, or 120 mg. In certain embodiments of the unit doses of a composition provided herein, the quantity of the oligomeric agent, e.g., ION904, in the unit dose is 60 mg to 120 mg.

[0484] In certain embodiments of the unit doses of a composition, e.g., pharmaceutical composition, containing an oligomeric agent, e.g., ION04, that contains a modified oligonucleotide (e.g., comprising a nucleobase sequence consisting of 12-40 nucleosides) having a nucleobase sequence complementary to a nucleobase sequence of an equal length target region in an AGT nucleic acid, e.g., a human AGT nucleic acid such as, e.g., SEQ ID NO: 1 or 2, the unit dose is in a single-dose container or the unit dose is in a multi-dose container. In certain embodiments, the container is a vial, tube or ampule. In certain embodiments, the unit dose is in a single dose container, such as, for example, a syringe, e.g., a pre-filled syringe, or cartridge. In certain embodiments, a unit dose is contained within a medical device, e.g., an autoinjector or pen injector. In certain embodiments, a multi-dose container contains 2-12 unit doses, 2-11 unit doses, 2-10 unit doses, 2-9 unit doses, 2-8 unit doses, 2-7 unit doses, 2-6 unit doses, 2-5 unit doses, 2-4 unit doses, 2-3 unit doses, 12 unit doses, 11 unit doses, 10 unit doses, 9 unit doses, 8 unit doses, 7 unit doses, 6 unit doses, 5 unit doses, 4 unit doses, 3 unit doses, or 2 unit doses. In certain embodiments, an autoinjector or pen injector contains 1-12 unit doses, 1-11 unit doses, 1-10 unit doses, 1-9 unit doses, 1-8 unit doses, 1-7 unit doses, 1-6 unit doses, 1-5 unit doses, 1-4 unit doses, 1-3 unit doses, 1-2 unit doses, 12 unit

doses, 11 unit doses, 10 unit doses, 9 unit doses, 8 unit doses, 7 unit doses, 6 unit doses, 5 unit doses, 4 unit doses, 3 unit doses, 2 unit doses or 1 unit dose.

[0485] C. Kits

[0486] Also provided herein are kits containing any unit dose described herein of an oligomeric agent (or salt thereof), e.g., ION904, that contains a modified oligonucleotide (e.g., comprising a nucleobase sequence consisting of 12-40 nucleosides) having a nucleobase sequence complementary to a nucleobase sequence of an equal length target region in an AGT nucleic acid, e.g., a human AGT nucleic acid such as, e.g., SEQ ID NO: 1 or 2. Further provided herein are kits containing any unit dose described herein of a composition, e.g., pharmaceutical composition, comprising or consisting of, or consisting essentially of, an oligomeric agent, e.g., ION904, that contains a modified oligonucleotide (e.g., comprising a nucleobase sequence consisting of 12-40 nucleosides) having a nucleobase sequence complementary to a nucleobase sequence of an equal length target region in an AGT nucleic acid, e.g., a human AGT nucleic acid such as, e.g., SEQ ID NO: 1 or 2. In certain embodiments, a kit contains the unit dose and instructions for use of the unit dose. In certain embodiments, a kit contains the unit dose, instructions for use of the unit dose, and means for administering the unit dose. In certain embodiments, the instructions are for use in reducing the amount of AGT RNA and/or AGT protein in a subject having or at risk for heart failure (such as HFrEF, HFmrEF, HFimpEF or HFpEF). In certain embodiments, the instructions are for use in reducing the amount of AGT RNA and/or AGT protein in a subject having or at risk for HFrEF. In certain embodiments, the instructions are for use in treating, or ameliorating one or more symptoms of, heart failure in a subject having or at risk for heart failure (such as HFrEF, HFmrEF, HFimpEF or HFpEF). In certain embodiments, the instructions are for use in treating, or ameliorating one or more symptoms of, heart failure in a subject having or at risk for HFrEF, HFmrEF.

[0487] IV. METHODS

[0488] In certain embodiments, methods described herein include administering an oligomeric agent (e.g., a unit dose) that contains a modified oligonucleotide (e.g., comprising a nucleobase sequence consisting of 16-30 nucleosides) having a nucleobase sequence complementary to a nucleobase sequence of an equal length target region in an AGT nucleic acid, e.g., a human AGT nucleic acid such as, e.g., SEQ ID NO: 1 or 2, to a cell or subject. In certain embodiments, the oligomeric agent is any such oligomeric agent described herein and/or containing any such oligonucleotide described

herein. In certain embodiments, a certain dose of the oligomeric agent is administered to the cell or subject.

[0489] In certain embodiments, provided herein are methods of administering an oligomeric agent, e.g., ION904, that contains a modified oligonucleotide (e.g., comprising a nucleobase sequence consisting of 16-30 nucleosides) having a nucleobase sequence complementary to a nucleobase sequence of an equal length target region in an AGT nucleic acid, e.g., a human AGT nucleic acid such as, e.g., SEQ ID NO: 1 or 2, which include administering a certain dose (e.g., a unit dose) of the oligomeric agent to a cell or subject. In certain embodiments, the oligomeric agent is ION904. In certain embodiments, the dose of the oligomeric agent, e.g., ION904, is a fixed dose. In certain embodiments, the dose of the oligomeric agent, e.g., ION904, is a weight-based dose. Also provided are methods for reducing the amount of AGT RNA and/or AGT protein in a cell or a subject having or at risk for heart failure, or for treating, and/or ameliorating at least one symptom of heart failure in, a subject having or at risk for heart failure, that include administering a certain dose (e.g., a unit dose) of such an oligomeric agent, e.g., ION904, to the subject. In certain embodiments, the dose of the oligomeric agent, e.g., ION904, is a fixed dose. In certain embodiments, the dose of the oligomeric agent, e.g., ION904, is a weight-based dose.

[0490] In certain embodiments, the oligomeric agent is contained in a composition such as a pharmaceutical composition, e.g., a pharmaceutical formulation. In certain embodiments, the composition contains a pharmaceutically acceptable carrier or excipient. In certain embodiments, the pharmaceutical composition consists of an oligomeric agent and a pharmaceutically acceptable carrier or excipient. In certain embodiments, the oligonucleotide of the oligomeric agent is single-stranded. In certain embodiments, the oligonucleotide of the oligomeric agent is a single-stranded antisense agent, and in certain embodiments is a single-stranded RNase H agent. In certain embodiments, the composition is a pharmaceutical composition consisting of an oligomeric agent consisting of a single-stranded antisense agent, and optionally a conjugate group, and a pharmaceutically acceptable carrier or excipient.

[0491] In certain embodiments, the methods include administering an oligomeric agent that contains a modified oligonucleotide (e.g., comprising a nucleobase sequence consisting of 16-30 nucleosides) having a nucleobase sequence at least 12, at least 13, at least 14, at least 15, or at least 16 contiguous nucleobases complementary to an equal length portion of nucleobases 2046-2061 of SEQ ID NO: 1 or nucleobases 14940-14955 of SEQ ID NO: 2. In certain embodiments, the nucleobase sequence of

the modified oligonucleotide includes at least 12, at least 13, at least 14, at least 15, or at least 16 contiguous nucleobases of SEQ ID NO: 3, 4 or 5. In certain embodiments, the nucleobase sequence of the modified oligonucleotide is SEQ ID NO: 3, 4 or 5. In certain embodiments, the oligomeric agent contains a conjugate group attached to the modified oligonucleotide. In certain embodiments, the conjugate group includes one or more GalNAc moieties (e.g., trishexylamino-(THA)-C6 GalNAc₃). In certain embodiments, the oligomeric agent consists of, or consists essentially of, the modified oligonucleotide and the conjugate group. In certain embodiments, the oligomeric agent comprises or consists of a modified oligonucleotide according to the following chemical notation (5' to 3'):

${}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 4); wherein,

A = an adenine nucleobase,

${}^m\text{C}$ = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

k = a cEt sugar moiety,

d = an unmodified DNA sugar moiety,

s = a phosphorothioate internucleoside linkage, and

• = a phosphodiester internucleoside linkage.

[0492] In certain embodiments, the methods include administering ION904 (represented in certain embodiments by Structure 1). ION904, and compositions containing ION904, includes any salt (e.g., pharmaceutically acceptable salt) of ION904, e.g., potassium, calcium, magnesium, and sodium salts (see, e.g., Structure 2), ester of ION904, or salts of such esters.

[0493] In certain embodiments, ION904 is represented by the following chemical notation (5' to 3'):

THA-C6-GalNAc₃- ${}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 5);

wherein,

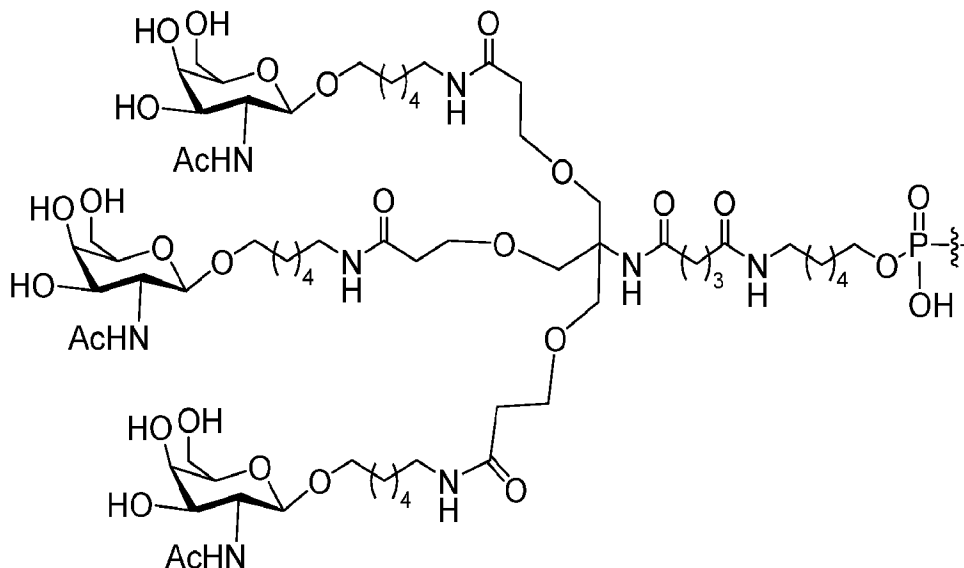
A = an adenine nucleobase,

${}^m\text{C}$ = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,
 k = a cEt sugar moiety,
 d = an unmodified DNA sugar moiety,
 s = a phosphorothioate internucleoside linkage,
 • = a phosphodiester internucleoside linkage, and
 THA-C6-GalNAc₃=



[0494] In certain embodiments, an oligomeric agent, e.g., ION904, is administered in a pharmaceutical composition. In certain embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or excipient. In certain embodiments, the pharmaceutical composition consists of, or consists essentially of, the oligomeric agent, e.g., ION904, and a pharmaceutically acceptable carrier or excipient. In certain embodiments, the pharmaceutical composition comprises, consists of, or consists essentially of a sterile saline solution and the oligomeric agent, e.g., ION904. In certain embodiments, the sterile saline is pharmaceutical grade saline. In certain embodiments, the pharmaceutical composition comprises, consists of, or consists essentially of sterile water and the oligomeric agent, e.g., ION904. In certain embodiments, the sterile water is pharmaceutical grade water. In certain embodiments, the pharmaceutical composition comprises, consists of, or consists essentially of the oligomeric agent, e.g., ION904, in 2mM phosphate buffered isotonic saline, pH 7.4. As described herein, a dose or quantity of an oligomeric agent, e.g., ION904, in milligrams indicates the mass of the free acid form of the oligomeric agent, e.g., ION904. In aqueous solution, the free acid is in equilibrium with anionic and salt forms. However, for the purpose of calculating dose or quantity, it is assumed that the oligomeric agent,

e.g., ION904, exists as a solvent-free, sodium-acetate free, anhydrous, free acid. For example, where an oligomeric agent, e.g., ION904, is in solution comprising sodium (e.g., saline), the oligomeric agent, e.g., ION904, 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.

[0495] In certain embodiments, a dose (e.g., a unit dose) of an oligomeric agent provided herein, is a quantity of the oligomeric agent, e.g., ION904, effective to, when administered to a cell or subject, decrease the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 70%, at least 75%, at least 80%, or at least 85% compared to the amount or level of AGT RNA and/or AGT protein prior to any administration of the oligomeric agent (e.g., the baseline or pre-administration level of AGT in the cell or subject). In certain embodiments, the maximum decrease in the amount or level of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT protein) is less than 95%, or less than 94%, or less than 93%, or less than 92%, or less than 91%, or less than 90% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, the amount or level of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT protein) decreases no more than 85%, or no more than 86%, or no more than 87%, or no more than 88%, or no more than 89%, or no more than 90%, or no more than 91%, or no more than 92%, or no more than 93%, or no more than 94%, or no more than 95%, compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, a dose (e.g., a unit dose) of the oligomeric agent, e.g., ION904, is a quantity of the oligomeric agent effective to, when administered to a cell or subject, decrease the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, a dose (e.g., a unit dose) of the oligomeric agent, e.g., ION904, is a quantity of the oligomeric agent effective to, when administered to a cell or subject, decrease the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood,

serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 70%, at least 75%, at least 80% or at least 85% and less than 94% compared to the baseline amount or level of AGT RNA and/or AGT protein in a cell or subject. In certain embodiments, a dose (e.g., a unit dose) of the oligomeric agent, e.g., ION904, is a quantity of the oligomeric agent effective to, when administered to a cell or subject, decrease the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 70%, at least 75%, at least 80% or at least 85% and less than 93% compared to the baseline amount or level of AGT RNA and/or AGT protein in a cell or subject. In certain embodiments, a dose (e.g., a unit dose) of the oligomeric agent, e.g., ION904, is a quantity of the oligomeric agent effective to, when administered to a cell or subject, decrease the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 70%, at least 75%, at least 80% or at least 85% and less than 92% compared to the baseline amount or level of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, a dose (e.g., a unit dose) of the oligomeric agent, e.g., ION904, is a quantity of the oligomeric agent effective to, when administered to a cell or subject, decrease the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 70%, at least 75%, at least 80% or at least 85% and less than 91% compared to the baseline amount or level of AGT RNA and/or AGT protein in a cell or subject. In certain embodiments, a dose (e.g., a unit dose) of the oligomeric agent, e.g., ION904, is a quantity of the oligomeric agent effective to, when administered to a cell or subject, decrease the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 70%, at least 75%, at least 80% or at least 85% and less than 90% compared to the baseline amount or level of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, a dose (e.g., a unit dose) of the oligomeric agent, e.g., ION904, is a quantity of the oligomeric agent effective to, when administered to a cell or subject, decrease the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 70%, at least 75%, at least 80% or at

least 85% and less than 89% compared to the baseline amount or level of AGT RNA and/or AGT protein in the cell or subject.

[0496] In certain embodiments, a dose (e.g., a unit dose) of the oligomeric agent, e.g., ION904, is a quantity of the oligomeric agent effective to, when administered to a cell or subject, decrease the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 70% but less than 95%, less than 94%, less than 93%, less than 92%, less than 91%, less than 90%, less than 89%, less than 88%, or less than 85% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, a dose (e.g., a unit dose) of the oligomeric agent, e.g., ION904, is a quantity of the oligomeric agent effective to, when administered to a cell or subject, decrease the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 75% but less than 95%, less than 94%, less than 93%, less than 92%, less than 91%, less than 90%, less than 89%, less than 88%, or less than 85% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, a dose (e.g., a unit dose) of the oligomeric agent, e.g., ION904, is a quantity of the oligomeric agent effective to, when administered to a cell or subject, decrease the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 80% but less than 95%, less than 94%, less than 93%, less than 92%, less than 91%, less than 90%, less than 89%, less than 88%, or less than 85% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, a dose (e.g., a unit dose) of the oligomeric agent, e.g., ION904, is a quantity of the oligomeric agent effective to, when administered to a cell or subject, decrease the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by at least 85% but less than 95%, less than 94%, less than 93%, less than 92%, less than 91%, less than 90%, or less than 89% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, a dose (e.g., a unit dose) of the oligomeric agent, e.g., ION904, is a quantity of the oligomeric agent effective to, when administered to a cell or subject, decrease the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of

AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by 70%-90%, 70%-89%, 70%-88%, 70%-87%, 70%-86%, 70%-85%, 70%-84%, 70%-83%, 70%-82%, 70%-81%, 70%-80%, 75%-90%, 75%-89%, 75%-88%, 75%-87%, 75%-86%, 75%-85%, 75%-84%, 75%-83%, 75%-82%, 75%-81%, 75%-80%, 76%-90%, 76%-89%, 76%-88%, 76%-87%, 76%-86%, 76%-85%, 76%-84%, 76%-83%, 76%-82%, 76%-81%, 76%-80%, 77%-90%, 77%-89%, 77%-88%, 77%-87%, 77%-86%, 77%-85%, 77%-84%, 77%-83%, 77%-82%, 77%-81%, 77%-80%, 78%-90%, 78%-89%, 78%-88%, 78%-87%, 78%-86%, 78%-85%, 78%-84%, 78%-83%, 78%-82%, 78%-81%, 78%-80%, 79%-90%, 79%-89%, 79%-88%, 79%-87%, 79%-86%, 79%-85%, 79%-84%, 79%-83%, 79%-82%, 79%-81%, 79%-80%, 80%-90%, 80%-89%, 80%-88%, 80%-87%, 80%-86%, 80%-85%, 80%-84%, 80%-83%, 80%-82%, 81%-90%, 81%-89%, 81%-88%, 81%-87%, 81%-86%, 81%-85%, 81%-84%, 81%-83%, 81%-82%, 82%-90%, 82%-89%, 82%-88%, 82%-87%, 82%-86%, 82%-85%, 82%-84%, 82%-83%, 83%-90%, 83%-89%, 83%-88%, 83%-87%, 83%-86%, 83%-85%, 83%-84%, 84%-90%, 84%-89%, 84%-88%, 84%-87%, 84%-86%, 84%-85%, 85%-90%, 85%-89%, 85%-88%, 85%-87%, 85%-86%, 86%-90%, 86%-89%, 86%-88%, 86%-87%, 87%-90%, 87%-89%, 87%-88%, 88%-90%, or 88%-89% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, the dose (e.g., a unit dose) of the oligomeric agent is administered once every month (or once every four weeks), or once every 28 days, or once every two weeks, or once every week.

[0497] In certain embodiments, a dose (e.g., a unit dose) of the oligomeric agent, e.g., ION904, is a quantity of the oligomeric agent effective to treat, and/or ameliorate one or more symptoms of, heart failure, such as HFReEF, HFmrEF or HFpEF, but that does not significantly alter (e.g., decrease) systemic blood pressure (e.g., systolic blood or diastolic blood pressure) in a subject having, or at risk for, heart failure, including, for example, a subject having, or at risk for, heart failure who has hypotension (low blood pressure) or normotension (normal blood pressure). In certain embodiments, a significant alteration in systolic or diastolic blood pressure is a greater than about 10 mm Hg change in blood pressure, or a greater than about 11 mm Hg change in blood pressure, or a greater than about 12 mm Hg change in blood pressure, or a greater than about 13 mm Hg change in blood pressure, or a greater than about 14 mm Hg change in blood pressure, or a greater than about 15 mm Hg change in blood pressure. In certain embodiments, normal systolic blood pressure is within the range of about 90 mm Hg or 100 mm Hg to about 120 mm Hg or 125 mm Hg, and normal diastolic blood pressure is within the range of about 60 mm Hg and about 80 mm Hg. In certain

embodiments, low systolic blood pressure is less than about 90 mm Hg and low diastolic blood pressure is less than about 60 mm Hg. In certain embodiments, elevated systolic blood pressure is about 125 mm Hg to about 129 mm Hg and high systolic blood pressure (i.e., hypertension) is about 130 mm Hg or higher. In certain embodiments, a dose of the oligomeric agent, e.g., ION904, is a quantity of the oligomeric agent effective in treating, and/or ameliorating one or more symptoms of, HFrEF, but does not significantly alter (e.g., decrease) systemic blood pressure (e.g., systolic blood or diastolic blood pressure) in a subject having, or at risk for, HFrEF, including, for example, a subject having, or at risk for, heart failure who has hypotension or normal blood pressure.

[0498] In certain embodiments, a dose (e.g., a unit dose) of oligomeric agent, e.g., ION904, is a quantity of the oligomeric agent effective in treating, and/or ameliorating one or more symptoms of, heart failure, such as HFrEF, HFmrEF or HFpEF, but that does not significantly alter (e.g., increase) potassium levels (e.g., blood, serum or plasma potassium levels) in a subject having, or at risk for, heart failure (such as HFrEF, HFmrEF or HFpEF), including, for example, a subject having, or at risk for, heart failure who has hyperkalemia, renal dysfunction, or renal insufficiency, acute kidney injury (AKI), or chronic kidney disease (CKD). In certain embodiments, hyperkalemia is a high potassium level (e.g., serum potassium level) of greater than about 5.0 mEq/L or about 5.5 mEq/L, elevated serum potassium level is greater than about 4.0 mEq/L, and normal potassium levels are within the range of about 3.5 mEq/L to about 5.0 mEq/L. In certain embodiments, renal insufficiency is associated with an eGFR of less than about 90 ml/min/1.73 m² or less than about 100 ml/min/1.73 m² (or eGFR between 30 and 90 ml/min/1.73 m², ≤ 40 ml/min/1.73 m², ≤ 35 ml/min/1.73 m², or ≤ 30 ml/min/1.73 m²), stage 2 kidney disease is associated with an eGFR within the range of about 60 ml/min/1.73 m² to about 89 ml/min/1.73 m², stage 3 kidney disease is associated with an eGFR within the range of about 30 ml/min/1.73 m² to about 59 ml/min/1.73 m², stage 4 kidney disease is associated with an eGFR within the range of about 15 ml/min/1.73 m² to about 29 ml/min/1.73 m², and stage 5 kidney disease (kidney failure) is associated with an eGFR of less than about 15 ml/min/1.73 m². In certain embodiments, a dose (e.g., a unit dose) of oligomeric agent e.g., ION904, is a quantity of the oligomeric agent effective in treating, and/or ameliorating one or more symptoms of, HFrEF, but that does not significantly alter (e.g., increase) potassium levels (e.g., blood, serum or plasma potassium levels) in a subject having, or at risk for, HFrEF, including, for example, a subject having, or at risk for, HFrEF who has hyperkalemia, renal dysfunction, or renal insufficiency, acute kidney injury (AKI), or chronic kidney disease (CKD).

[0499] In certain embodiments, a dose (e.g., a unit dose) of oligomeric agent e.g., ION904, is a quantity of the oligomeric agent effective in treating, and/or ameliorating one or more symptoms of, heart failure, such as HFrEF, HFmrEF or HFpEF, but that does not significantly alter bradykinin homeostasis and/or increase bradykinin levels (e.g., blood, serum, or plasma bradykinin levels) in a subject having, or at risk for heart failure (such as HFrEF, HFmrEF or HFpEF), including, for example, a subject having, or at risk for heart failure who has pulmonary disease or angioedema. In certain embodiments, the dose (e.g., a unit dose) of oligomeric agent e.g., ION904, is a quantity of the oligomeric agent effective in treating, and/or ameliorating one or more symptoms of, HFrEF, but that does not significantly alter bradykinin homeostasis and/or increase bradykinin levels (e.g., blood, serum, or plasma bradykinin levels) in a subject having, or at risk for, HFrEF, including, e.g., a subject having, or at risk for heart failure who has pulmonary disease or angioedema.

[0500] In certain embodiments, a dose (e.g., a unit dose) of oligomeric agent e.g., ION904, is a quantity of the oligomeric agent that improves cardiac function, reduces cardiac dilation, reduces cardiac fibrosis, reverses or attenuates cardiac remodeling, and/or increases LVEF in a subject having, or at risk for, heart failure (such as HFrEF, HFmrEF or HFpEF). In certain embodiments a dose (e.g., a unit dose) of oligomeric agent e.g., ION904, is a quantity of the oligomeric agent that improves cardiac function, reduces cardiac dilation, reduces cardiac fibrosis, reverses or attenuates cardiac remodeling, and/or increases LVEF in a subject having, or at risk for, HFrEF. In certain embodiments, a dose (e.g., a unit dose) of oligomeric agent, e.g., ION904, is a quantity of the oligomeric agent that improves left ventricular end diastolic volume (LVEDV), improves left ventricle (LV) strain, improves a 6-minute walk test, and/or improves quality of life as assessed by patient reported outcomes of a subject having, or at risk for, heart failure. In certain embodiments, a dose (e.g., a unit dose) of oligomeric agent e.g., ION904, is a quantity of the oligomeric agent that improves left ventricular ESVi or LVESV of a subject having, or at risk for, heart failure (such as HFrEF, HFmrEF or HFpEF). In certain embodiments, a dose (e.g., a unit dose) of oligomeric agent e.g., ION904, is an amount of the oligomeric agent that improves ESVi or LVESV of a subject having, or at risk for, HFrEF. In certain embodiments, a dose (e.g., a unit dose) of oligomeric agent e.g., ION904, is a quantity of the oligomeric agent that decreases the level of NT-proBNP, BNP, high-sensitive cardiac troponin T (hs-cTnT), and/or cTnT in plasma of a subject having, or at risk for, heart failure (such as HFrEF, HFmrEF or HFpEF) compared to the level prior to administration of the oligomeric agent, or to the baseline level in a subject before any administration of the

oligomeric agent, e.g., ION904. In certain embodiments, a dose (e.g., a unit dose) of oligomeric agent e.g., ION904, is a quantity of the oligomeric agent that decreases the level of NT-proBNP, BNP, high-sensitive cardiac troponin T (hs-cTnT), and/or cTnT in plasma of a subject having, or at risk for, HFrEF compared to the level prior to administration of the oligomeric agent, or to the baseline level in a subject before any administration of the oligomeric agent, e.g., ION904. In certain embodiments, the dose (e.g., a unit dose) of the oligomeric agent is administered once every month (or once every four weeks), or once every 28 days, or once every two weeks, or once every week.

[0501] In certain embodiments, a dose (e.g., a unit dose) of an oligomeric agent, e.g., ION904, is a quantity of the oligomeric agent administered as a loading dose. In certain embodiments, administration of one or more loading dose is effective in achieving a desired condition in a subject, for example, a desired initial concentration of oligomeric agent, e.g., ION904. In certain embodiments, the quantity of oligomeric agent in a loading dose(s) is/are effective in decreasing the amount or level of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) compared to the amount or level of AGT RNA and/or AGT protein prior to administration of the loading dose of the oligomeric agent (e.g., the baseline or pre-administration level of AGT). In certain embodiments, a dose, e.g., a loading dose(s), is effective to decrease the amount or level of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) by 20%-95%, 20%-90%, 20%-89%, 20%-88%, 20%-87%, 20%-86%, 20%-85%, 20%-84%, 20%-83%, 20%-82%, 20%-81%, 20%-80%, 20%-79%, 20%-78%, 20%-77%, 20%-76%, 20%-75%, 20%-74%, 20%-73%, 20%-72%, 20%-71%, 20%-70%, 20%-65%, 20%-60%, 20%-55%, 20%-50%, 50%-95%, 50%-90%, 50%-89%, 50%-88%, 50%-87%, 50%-86%, 50%-85%, 50%-84%, 50%-83%, 50%-82%, 50%-81%, 50%-80%, 50%-79%, 50%-78%, 50%-77%, 50%-76%, 50%-75%, 50%-74%, 50%-73%, 50%-72%, 50%-71%, 50%-70%, 50%-65%, 50%-60%, 60%-95%, 60%-90%, 60%-89%, 60%-88%, 60%-87%, 60%-86%, 60%-85%, 60%-84%, 60%-83%, 60%-82%, 60%-81%, 60%-80%, 60%-79%, 60%-78%, 60%-77%, 60%-76%, 60%-75%, 60%-74%, 60%-73%, 60%-72%, 60%-71%, 60%-70%, 60%-65%, 70%-95%, 70%-90%, 70%-89%, 70%-88%, 70%-87%, 70%-86%, 70%-85%, 70%-84%, 70%-83%, 70%-82%, 70%-81%, 70%-80%, 80%-95%, 80%-90%, 80%-89%, 80%-88%, 80%-87%, 80%-86%, 80%-85%, 90%-95%, 90%-94%, 90%-93%, or 90%-92% compared to the amount or level of AGT

RNA and/or AGT protein prior to administration of the loading dose of the oligomeric agent. In certain embodiments, administration of the loading dose(s) is more effective to decrease the amount or level of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) than administration of a maintenance dose is to decrease the amount or level of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein). In certain embodiments, administration of a loading dose(s) is less effective in decreasing the amount or level of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) than administration of a maintenance dose is to decrease the amount or level of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein). In certain embodiments, the quantity of the oligomeric agent, e.g., ION904, in a loading dose is greater than the quantity of the oligomeric agent, e.g., ION904, in a maintenance dose. In certain embodiments, the quantity of the oligomeric agent, e.g., ION904, in a loading dose is less than the quantity of the oligomeric agent, e.g., ION904, in a maintenance dose. In certain embodiments, a loading dose of the oligomeric agent is administered once every month (or once every four weeks), or once every 28 days, or once every two weeks, or once every week. In certain embodiments, 2 or more loading doses of the oligomeric agent are administered, for example, one loading dose administered each week or each 14 days.

[0502] In certain embodiments, a dose (e.g., a unit dose) of an oligomeric agent, e.g., ION904, is a quantity of the oligomeric agent administered as a maintenance dose. In certain embodiments, administration of the maintenance dose is effective in maintaining a desired condition in a subject that results from administration of the loading dose(s). In certain embodiments, administration of the maintenance dose is effective in maintaining an amount or level of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) that is less than the amount or level of AGT RNA and/or AGT protein prior to administration of the loading dose of the oligomeric agent (e.g., the baseline or pre-administration level of AGT). In certain embodiments, administration of the maintenance dose is effective in maintaining an amount or level of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the

circulating level of AGT RNA and/or AGT protein) that is about the same as the amount or level of AGT RNA and/or AGT protein after administration of the loading dose, that is less than the amount or level of AGT RNA and/or AGT protein after administration of the loading dose, or that is more than the amount or level of AGT RNA and/or AGT protein after administration of the loading dose but less than the amount or level of AGT RNA and/or AGT protein prior to administration of the loading dose of the oligomeric agent (e.g., the baseline or pre-administration level of AGT). In certain embodiments, the quantity of the oligomeric agent, e.g., ION904, in a maintenance dose is greater than the quantity of the oligomeric agent, e.g., ION904, in a loading dose. In certain embodiments, the quantity of the oligomeric agent, e.g., ION904, in a maintenance dose is less than the quantity of the oligomeric agent, e.g., ION904, in a loading dose. In certain embodiments, a maintenance dose of an oligomeric agent is administered once every month (or once every four weeks), or once every 28 days, or once every two weeks, or once every week.

[0503] In certain embodiments, the quantity of an oligomeric agent, e.g., ION904, in a dose (e.g., a unit dose) is within the range of about 15 mg to about 200 mg, about 20 mg to about 200 mg, about 40 mg to about 150 mg, about 60 mg to about 150 mg, about 60 mg to about 140 mg, about 65 mg to about 140 mg, about 70 mg to about 140 mg, about 75 mg to about 120 mg, about 80 mg to about 120 mg, about 85 mg to about 120 mg, about 90 mg to about 120 mg, about 95 mg to about 120 mg, about 100 mg to about 120 mg, about 60 mg to about 110 mg, about 65 mg to about 110 mg, about 70 mg to about 110 mg, about 75 mg to about 110 mg, about 80 mg to about 110 mg, about 85 mg to about 110 mg, about 90 mg to about 110 mg, about 95 mg to about 110 mg, about 100 mg to about 110 mg, about 60 mg to about 100 mg, about 65 mg to about 100 mg, about 70 mg to about 100 mg, about 75 mg to about 100 mg, about 80 mg to about 100 mg, about 85 mg to about 100 mg, about 90 mg to about 100 mg, or about 95 mg to about 100 mg. In certain embodiments, the dose (e.g., a unit dose) of the oligomeric agent, e.g., ION904, is administered once every month (or once every four weeks), or once every 28 days, or once every two weeks, or once every week.

[0504] In certain embodiments, the quantity of an oligomeric agent, e.g., ION904, in a dose (e.g., a unit dose) is within the range of about 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 dose (e.g., a unit dose) of the oligomeric agent, e.g., ION904, is administered once every month (or once every four weeks), or once every 28 days, or once every two weeks, or once every week.

[0505] In certain embodiments, the quantity of an oligomeric agent, e.g., ION904, in a dose (e.g., a unit dose) is at least about 20 mg and less than 200 mg, at least about 20 mg and less than 195 mg, at least about 20 mg and less than 190 mg, at least about 20 mg and less than 185 mg, at least about 20 mg and less than 180 mg, at least about 20 mg and less than 175 mg, at least about 20 mg and less than 170 mg, at least about 20 mg and less than 165 mg, at least about 20 mg and less than 160 mg, at least about 20 mg and less than 155 mg, at least about 20 mg and less than 150 mg, at least about

20 mg and less than 145 mg, at least about 20 mg and less than 140 mg, at least about 20 mg and less than 135 mg, at least about 20 mg and less than 130 mg, at least about 20 mg and less than 125 mg, at least about 20 mg and less than 120 mg, at least about 20 mg and less than 115 mg, at least about 20 mg and less than 110 mg, at least about 20 mg and less than 105 mg, at least about 20 mg and less than 100 mg, at least about 20 mg and less than 95 mg, at least about 20 mg and less than 90 mg, at least about 20 mg and less than 85 mg, at least about 20 mg and less than 80 mg, at least about 20 mg and less than 75 mg, at least about 20 mg and less than 70 mg, at least about 20 mg and less than 65 mg, at least about 20 mg and less than 60 mg, at least about 20 mg and less than 55 mg, at least about 20 mg and less than 50 mg, at least about 20 mg and less than 45 mg, at least about 20 mg and less than 40 mg, at least about 20 mg and less than 35 mg, or at least about 20 mg and less than 30 mg. In certain embodiments, the dose (e.g., a unit dose) of the oligomeric agent, e.g., ION904, is administered every month (or once every four weeks), or once every 28 days, or once every two weeks, or once every week.

[0506] In certain embodiments, the quantity of an oligomeric agent, e.g., ION904, in a dose (e.g., a unit dose) is at least about 20 mg and less than about 200 mg, at least about 20 mg and less than about 195 mg, at least about 20 mg and less than about 190 mg, at least about 20 mg and less than about 185 mg, at least about 20 mg and less than about 180 mg, at least about 20 mg and less than about 175 mg, at least about 20 mg and less than about 170 mg, at least about 20 mg and less than about 165 mg, at least about 20 mg and less than about 160 mg, at least about 20 mg and less than about 155 mg, at least about 20 mg and less than about 150 mg, at least about 20 mg and less than about 145 mg, at least about 20 mg and less than about 140 mg, at least about 20 mg and less than about 135 mg, at least about 20 mg and less than about 130 mg, at least about 20 mg and less than about 125 mg, at least about 20 mg and less than about 120 mg, at least about 20 mg and less than about 115 mg, at least about 20 mg and less than about 110 mg, at least about 20 mg and less than about 105 mg, at least about 20 mg and less than about 100 mg, at least about 20 mg and less than about 95 mg, at least about 20 mg and less than about 90 mg, at least about 20 mg and less than about 85 mg, at least about 20 mg and less than about 80 mg, at least about 20 mg and less than about 75 mg, at least about 20 mg and less than about 70 mg, at least about 20 mg and less than about 65 mg, at least about 20 mg and less than about 60 mg, at least about 20 mg and less than about 55 mg, at least about 20 mg and less than about 50 mg, at least about 20 mg and less than about 45 mg, at least about 20 mg and less than about 40 mg, at least about 20 mg and less than

about 35 mg, or at least about 20 mg and less than about 30 mg. In certain embodiments, the dose (e.g., a unit dose) of the oligomeric agent, e.g., ION904, is administered once every month (or once every four weeks), or once every 28 days, or once every two weeks, or once every week.

[0507] In certain embodiments, the quantity of the oligomeric agent, e.g., ION904, in a dose (e.g., a unit dose) is about 15 mg, is or is about 20 mg, about 30 mg, about 40 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, or about 150 mg. In certain embodiments of doses provided herein, the quantity of the oligomeric agent, e.g., ION904, in the dose is 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, or about 110 mg. In certain embodiments, the dose (e.g., a unit dose) of the oligomeric agent, e.g., ION904, is administered once every month (or once every four weeks), or once every 28 days, or once every two weeks, or once every week.

[0508] In certain embodiments, the quantity of the oligomeric agent, e.g., ION904, in a dose (e.g., a unit dose) is 15 mg, 20 mg, 30 mg, 40 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, or 150 mg. In certain embodiments of doses provided herein, the quantity of the oligomeric agent, e.g., ION904, in the dose is 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, or 110 mg. In certain embodiments, the dose (e.g., a unit dose) of the oligomeric agent, e.g., ION904, is administered once every month (or once every four weeks), or once every 28 days, or once every two weeks, or once every week.

[0509] In certain embodiments, the quantity of the oligomeric agent, e.g., ION904, in a dose (e.g., a unit dose) is within the range of about 60 mg to about 110 mg, about 75 mg to about 110 mg, about 85 mg to about 110 mg, about 90 mg to about 110 mg, about 95 mg to about 110 mg, about 100 mg to about 110 mg, about 80 mg to about 100 mg, about 85 mg to about 100 mg, or about 90 mg to about 100 mg. In certain embodiments, the quantity of the oligomeric agent, e.g., ION904, in a dose (e.g., a unit dose) is 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, or about 120 mg. In certain embodiments, the quantity of the oligomeric agent, e.g., ION904, in a dose (e.g., a unit dose) is 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 105 mg, 110 mg, or 120 mg. In certain embodiments, the quantity of the oligomeric agent, e.g., ION904, in a dose (e.g., a unit

dose) is 80 mg to 120 mg. In certain embodiments, the dose (e.g., a unit dose) of the oligomeric agent is administered once every month, once every four weeks, or once every 28 days.

[0510] A. Dosing Regimens

[0511] In certain embodiments, provided herein are methods (and compositions for use in the methods) of administering an oligomeric agent that contains a modified oligonucleotide (e.g., comprising a nucleobase sequence consisting of 16-30 nucleosides) having a nucleobase sequence complementary to a nucleobase sequence of an equal length target region in an AGT nucleic acid, e.g., a human AGT nucleic acid such as, e.g., SEQ ID NO: 1 or 2, which include administering a quantity (e.g., dose, e.g., a unit dose) of the oligomeric agent, e.g., ION904, to a subject one time, at least two times, two or more times, or a plurality of times. In certain embodiments, the oligomeric agent, e.g., ION904, is administered to a subject more than once, e.g., at least two times or two or more times, and the administrations of the oligomeric agent are separated by a period of time in a dosing regimen. In certain embodiments, the doses of oligomeric agent, e.g., ION904, administered at separate times can be the same or different. In certain embodiments, the oligomeric agent is administered repeatedly for a certain period of time (e.g., treatment period or treatment duration). In certain embodiments, the oligomeric agent is administered repeatedly for an indeterminate period of time (e.g., no defined end time). In certain embodiments, the dose(s) (e.g., a unit dose) is/are any of the particular doses or amounts described herein. In certain embodiments, methods for (and compositions for use in the methods) of administering an oligomeric agent, e.g., ION904, provide a dosing regimen for reducing the level or amount of AGT RNA and/or AGT protein in a subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein). In certain embodiments, methods (and compositions for use in the methods) of administering an oligomeric agent, e.g., ION904, provide a dosing regimen for treating a subject having or at risk for heart failure, such as HFrEF, HFpEF, or HFmrEF. In certain embodiments, a subject has or is at risk for HFrEF. In certain embodiments of the methods of administering an oligomeric agent, e.g., that contains a modified oligonucleotide (e.g., comprising a nucleobase sequence consisting of 16-30 nucleosides) having a nucleobase sequence complementary to a nucleobase sequence of an equal length target region in an AGT nucleic acid, e.g., a human AGT nucleic acid such as, e.g., SEQ ID NO: 1 or 2, to a subject, the subject has or is at risk for heart failure, such as HFrEF, HFpEF, or HFmrEF. In certain embodiments, the subject has or is at risk for HFrEF. In certain embodiments, the subject is, or is at risk of being, susceptible to

adverse side effects of existing RAAS inhibitor therapies, including, but not limited to, ACE inhibitors (ACEi), ARB, ARNi, and MRA. In certain embodiments, the subject is unable to tolerate treatment with optimal, Guideline-recommended target doses and/or dosing frequencies of RAAS inhibitors (e.g., ACEi, ARB, ARNi, MRA). In certain embodiments, the subject has renal dysfunction, renal insufficiency (including, e.g., AKI, CKD), hypotension, low-to-normal blood pressure, and/or pulmonary disease. In certain embodiments, the subject has or is at risk of having hyperkalemia, angioedema or asthma.

[0512] In certain embodiments of methods of administering an oligomeric agent (e.g., a unit dose of an oligomeric agent) that contains a modified oligonucleotide (e.g., comprising a nucleobase sequence consisting of 16-30 nucleosides) having a nucleobase sequence complementary to a nucleobase sequence of an equal length target region in an AGT nucleic acid, e.g., a human AGT nucleic acid such as, e.g., SEQ ID NO: 1 or 2, the oligomeric agent, e.g., ION904, or composition containing it, is administered once every month. In certain embodiments, the oligomeric agent, e.g., ION904, or composition containing it, is administered once every 4 weeks. In certain embodiments, the oligomeric agent, e.g., ION904, is administered to a subject at an interval of once a month, an interval of once a quarter, or an interval of biannually. In certain embodiments, the oligomeric agent, e.g., ION904, is administered to a subject at an interval of about once a week, an interval of about once every 2 weeks, an interval of about once every 3 weeks, an interval of about once every 4 weeks, an interval of about once every 5 weeks, or an interval of about once every 6 weeks. In certain embodiments, the oligomeric agent, e.g., ION904, or composition containing it, is administered 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, once every 8 weeks, once every 9 weeks, once every 10 weeks, once every 11 once every 12 weeks. In certain embodiments, the oligomeric agent, e.g., ION904, or composition containing it, is administered once every 28 days. In certain embodiments, the oligomeric agent, e.g., ION904, or composition containing it, is administered once every 84 days, once every 56 days, once every 30 days, once every 28 days, once every 20 days, or once every 14 days. In certain embodiments, the oligomeric agent, e.g., ION904, or composition containing it, is administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 times or more.

[0513] In certain embodiments, the quantity of the oligomeric agent, e.g., ION904, administered according to any regimen described herein is within the range of about 60 mg to about 120 mg, about 65 mg to about 120 mg, about 70 mg to about 120 mg, about 75 mg to about 120 mg, about 80

mg to about 120 mg, about 85 mg to about 120 mg, about 90 mg to about 120 mg, about 95 mg to about 120 mg, about 100 mg to about 120 mg, 60 mg to about 110 mg, about 65 mg to about 110 mg, about 70 mg to about 110 mg, about 75 mg to about 110 mg, about 80 mg to about 110 mg, about 85 mg to about 110 mg, about 90 mg to about 110 mg, about 95 mg to about 110 mg, about 100 mg to about 110 mg, about 60 mg to about 100 mg, about 65 mg to about 100 mg, about 70 mg to about 100 mg, about 75 mg to about 100 mg, about 80 mg to about 100 mg, about 85 mg to about 100 mg, about 90 mg to about 100 mg, or about 95 mg to about 100 mg. In certain embodiments, the quantity of the oligomeric agent, e.g., ION904, administered 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, or about 120 mg. In certain embodiments, the quantity of the oligomeric agent, e.g., ION904, administered is 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 105 mg, 110 mg, or 120 mg. In any of the foregoing embodiments, the oligomeric agent, e.g., ION904, or composition containing it, can be administered by a syringe. In any of the foregoing embodiments, the oligomeric agent, e.g., ION904, or composition containing it, can be administered subcutaneously.

[0514] In certain embodiments of the methods of administering an oligomeric agent (e.g., a unit dose of an oligomeric agent) that contains a modified oligonucleotide (e.g., comprising a nucleobase sequence consisting of 16-30 nucleosides) having a nucleobase sequence complementary to a nucleobase sequence of an equal length target region in an AGT nucleic acid, e.g., a human AGT nucleic acid such as, e.g., SEQ ID NO: 1 or 2, the oligomeric agent, e.g., ION904, or composition containing it, is administered to a subject about once every 2 weeks for at least about 52 weeks, at least about 26 weeks, or at least about 13 weeks. In certain embodiments, the oligomeric agent, e.g., ION904, is administered to a subject about once every 3 weeks for at least about 52 weeks, at least about 26 weeks, or at least about 13 weeks. In certain embodiments, the oligomeric agent, e.g., ION904, is administered to a subject about once every 4 weeks for at least about 52 weeks, at least about 26 weeks, or at least about 13 weeks. In certain embodiments, the oligomeric agent, e.g., ION904, is administered to a subject about once every 5 weeks for at least about 52 weeks, or at least about 26 weeks. In certain embodiments, the oligomeric agent, e.g., ION904, is administered to a subject about every 6 weeks for at least about 52 weeks, at least about 26 weeks, or at least about 13 weeks. In certain embodiments, the oligomeric agent, e.g., ION904, is administered to a subject about once every 4 weeks for an indeterminate period of time. In certain embodiments,

administration of the oligomeric agent, e.g., ION904, is repeated monthly. In certain embodiments, the oligomeric agent, e.g., ION904, is administered to a subject once a month for at least about 3 months. In certain embodiments, the oligomeric agent, e.g., ION904, is administered to a subject once a month for at least about 6 months. In certain embodiments, the oligomeric agent, e.g., ION904, is administered to a subject once a month for at least about 9 months. In certain embodiments, the oligomeric agent, e.g., ION904, is administered to a subject once a month for at least about 12 months. In certain embodiments, the oligomeric agent, e.g., ION904, is administered to a subject once a month for at least about 15 months. In certain embodiments, the oligomeric agent, e.g., ION904, is administered to a subject once a month for at least about 24 months. In certain embodiments, the oligomeric agent, e.g., ION904, is administered to a subject once a month for an indeterminate amount of time.

[0515] In certain embodiments of the methods of administering an oligomeric agent (e.g., a unit dose of an oligomeric agent) that contains a modified oligonucleotide (e.g., comprising a nucleobase sequence consisting of 16-30 nucleosides) having a nucleobase sequence complementary to a nucleobase sequence of an equal length target region in an AGT nucleic acid, e.g., a human AGT nucleic acid such as, e.g., SEQ ID NO: 1 or 2, the oligomeric agent, e.g., ION904, or composition containing it, is administered to a subject once about every 21 days, once about every 28 days, or once every 30 days. In certain embodiments, the oligomeric agent, e.g., ION904, is administered to a subject about every 21-28 days for at least about 90 days, at least about 120 days, at least about 180 days or at least about 365 days. In certain embodiments, the oligomeric agent, e.g., ION904, is administered to a subject every 28 days for at least about 90 days, at least about 120 days, at least about 180 days or at least about 365 days. In certain embodiments, the oligomeric agent, e.g., ION904, is administered to a subject every 28 days for an indeterminate period of time.

[0516] In certain embodiments, a method comprises administering to a subject about 60 mg of oligomeric agent, e.g., ION904, about once every 4 weeks. In certain embodiments, a method comprises administering to a subject 60 mg of oligomeric agent, e.g., ION904, once every 4 weeks. In certain embodiments a method comprises administering to a subject about 80 mg of oligomeric agent, e.g., ION904, about once every 4 weeks. In certain embodiments a method comprises administering to a subject 80 mg of oligomeric agent, e.g., ION904, once every 4 weeks. In certain embodiments a method comprises administering to a subject about 60 mg of oligomeric agent, e.g., ION904, subcutaneously about once every 4 weeks. In certain embodiments a method comprises

administering to a subject 60 mg of oligomeric agent, e.g., ION904, subcutaneously once every 4 weeks. In certain embodiments a method comprises administering to a subject about 80 mg of oligomeric agent, e.g., ION904, subcutaneously about once every 4 weeks. In certain embodiments a method comprises administering to a subject 80 mg of oligomeric agent, e.g., ION904, subcutaneously once every 4 weeks.

[0517] In certain embodiments, a method comprises administering to a subject about 90 mg of oligomeric agent, e.g., ION904, about once every 4 weeks. In certain embodiments, a method comprises administering to a subject 90 mg of oligomeric agent, e.g., ION904, once every 4 weeks. In certain embodiments a method comprises administering to a subject about 100 mg of oligomeric agent, e.g., ION904, about once every 4 weeks. In certain embodiments a method comprises administering to a subject 100 mg of oligomeric agent, e.g., ION904, once every 4 weeks. In certain embodiments a method comprises administering to a subject about 90 mg of oligomeric agent, e.g., ION904, subcutaneously about once every 4 weeks. In certain embodiments a method comprises administering to a subject 90 mg of oligomeric agent, e.g., ION904, subcutaneously once every 4 weeks. In certain embodiments a method comprises administering to a subject about 100 mg of oligomeric agent, e.g., ION904, subcutaneously about once every 4 weeks. In certain embodiments a method comprises administering to a subject 100 mg of oligomeric agent, e.g., ION904, subcutaneously once every 4 weeks.

[0518] In certain embodiments, methods comprise administering the oligomeric agent, e.g., ION904 (e.g., a unit dose of the oligomeric agent), for as long as required to decrease the amount or level of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) to a desired level and/or to maintain a desired amount or level of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein). In certain embodiments, methods comprise administering the oligomeric agent, e.g., ION904 (e.g., a unit dose of the oligomeric agent), for as long as the subject needs treatment for, and/or amelioration of one or more symptoms of, heart failure, such as HFrEF, HFpEF, or HFmrEF.

[0519] In certain embodiments of the methods of administering an oligomeric agent, e.g., ION904 (e.g., a unit dose of the oligomeric agent), the method includes administration of first loading and subsequent maintenance doses of the oligomeric agent which are the same dose. In certain

embodiments, the oligomeric agent (e.g., a unit dose), e.g., ION904, is administered one or more, at least two, two or more, or a plurality of times over a period of time (e.g., the treatment period). In certain embodiments, the quantity of oligomeric agent, e.g., ION904, administered each time is the same, i.e., the same dose is administered each time.

[0520] In certain embodiments, the quantity of oligomeric agent, e.g., ION904, at different time is not the same, i.e., different doses are administered at different times. For example, in certain embodiments, the quantity of oligomeric agent in the doses administered increases over time or decreases over time in the treatment period. In certain embodiments, a loading dose of the oligomeric agent, e.g., ION904, is administered at the start of treatment period and the dose reduces an amount or level of AGT RNA and/or AGT protein in the subject compared to the amount or level of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) prior to administration of the dose (e.g., a baseline or pre-administration amount or level of AGT RNA and/or AGT protein). The number of administrations of the oligomeric agent, e.g., ION904, during a period of time can vary depending on the desired outcome, for example, reducing the amount or level of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) or ameliorating one or more symptoms of heart failure in the subject. In certain embodiments, the amount or level of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) decreases about 60%-90%, about 60%-89%, about 60%-85%, about 60%-80%, about 60%-75%, about 65%-90%, about 65%-89%, about 65%-85%, about 65%-80%, about 65%-75%, about 70%-90%, about 70%-89%, about 70%-85%, about 70%-80%, or about 70%-75% within about 2-3 weeks after administration of a dose compared to the amount or level of AGT protein in the subject prior to any administration of the dose (e.g., the baseline amount or level). In certain embodiments, a dose of the oligomeric agent is administered to the subject one or more times during a treatment period. In certain embodiments, a loading dose of oligomeric agent is administered once, about 2 times, about 3 times, about 4 times, to achieve the level of AGT protein in the subject. In certain embodiments, subsequent maintenance dose(s) are regularly administered to maintain the effect. In certain embodiments, the same dose is administered each time. In certain embodiments, different doses may be administered at different times in the loading treatment period, followed by same

doses administered at same interval in the maintenance treatment period. In certain embodiments, the duration of the period of time (treatment period) is about 3 months, about 6 months, about 9 months, about 12 months, about 15 months, about 24 months, about 2 years, about 3 years, about 4 years, or about 5 years or more. In certain embodiments, the amount or level of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) decreases about 60%-90%, about 60%-89%, about 60%-85%, about 60%-80%, about 60%-75%, about 65%-90%, about 65%-89%, about 65%-85%, about 65%-80%, about 65%-75%, about 70%-90%, about 70%-89%, about 70%-85%, about 70%-80%, or about 70%-75% within about 2-3 weeks after administration of a first dose compared to the amount or level of AGT RNA and/or AGT protein in the subject prior to administration of the first dose. In certain embodiments, the amount or level of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) is maintained through the duration of the period of subsequently administered doses at about the same level as, or a lower level than, the level achieved about 2-3 weeks after the first administration of the dose of oligomeric agent. In certain embodiments, a method comprises administering to a subject about 60 mg of ION904 about once every 4 weeks. In certain embodiments, a method comprises administering to a subject 60 mg of ION904 once every 4 weeks. In certain embodiments a method comprises administering to a subject about 80 mg of ION904 about once every 4 weeks. In certain embodiments a method comprises administering to a subject 80 mg of ION904 once every 4 weeks. In certain embodiments, a method comprises administering to a subject about 90 mg of ION904 about once every 4 weeks. In certain embodiments, a method comprises administering to a subject 90 mg of ION904 once every 4 weeks. In certain embodiments a method comprises administering to a subject about 100 mg of ION904 about once every 4 weeks. In certain embodiments a method comprises administering to a subject 100 mg of ION904 once every 4 weeks.

[0521] In certain embodiments, the oligomeric agent, e.g., ION904, or composition containing it, is administered parenterally. In certain embodiments, the oligomeric agent, e.g., ION904, is administered subcutaneously.

[0522] 1. Loading and Maintenance Doses

[0523] In certain embodiments of the methods (and compositions for use in the methods) of administering an oligomeric agent, e.g., ION904 (e.g., a unit dose) that contains a modified

oligonucleotide (e.g., comprising a nucleobase sequence consisting of 16-30 nucleosides) having a nucleobase sequence complementary to a nucleobase sequence of an equal length target region in an AGT nucleic acid, e.g., a human AGT nucleic acid such as, e.g., SEQ ID NO: 1 or 2, a quantity of the oligomeric agent is administered as a loading dose and/or a maintenance dose. In certain embodiments, methods comprise administering one or more loading dose of the oligomeric agent, e.g., ION904, to a subject and subsequently administering one or more maintenance dose to the subject. In certain embodiments, the quantity of oligomeric agent in a loading dose and a maintenance dose is the same. In certain embodiments, the quantity of oligomeric agent in a loading dose and the quantity of oligomeric agent in a maintenance dose are different. In certain embodiments, the quantity of oligomeric agent in a loading dose is greater than the quantity of oligomeric agent in a maintenance dose. In certain embodiments, the quantity of oligomeric agent in a loading dose is less than the quantity of oligomeric agent in a maintenance dose. In certain embodiments, the quantity of oligomeric agent in each maintenance dose administered to a subject is the same. In certain embodiments, the quantity of oligomeric agent in two or more of the maintenance doses administered to a subject is not the same. In certain embodiments, the quantity of oligomeric agent in a maintenance dose administered to a subject two or more, or at least two, times differs and increases in one or more additional administrations given over time or decreases in one or more additional administrations given over time.

[0524] In certain embodiments, methods comprise administering at least 1 loading dose, 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 of the oligomeric agent, e.g., ION904. In certain embodiments, methods comprise administering 1, 2, 3, 4, or 5, loading doses of the oligomeric agent, e.g., ION904. In certain embodiments, methods comprise administering a loading dose of the oligomeric agent, e.g., ION904, about every day, every two days, every three days, every week, about every 2 weeks, or about every 3 weeks. In certain embodiments, methods comprise administering an initial loading dose of the oligomeric agent, e.g., ION904, and administering a second loading dose about 1 week after administering the initial loading dose. In certain embodiments, a first loading dose is the sole loading dose of the oligomeric agent.

[0525] In certain embodiments, methods comprise administering at least 1 maintenance dose, at least 2 maintenance doses, at least 3 maintenance doses, at least 4 maintenance doses, at least 5 maintenance doses, at least 6 maintenance doses of the oligomeric agent, at least 9 maintenance

doses, at least 12 maintenance doses, at least 18 maintenance doses of the oligomeric agent, at least 24 maintenance doses, at least 36 maintenance doses, or at least 60 maintenance doses or more of the oligomeric agent e.g., ION904. In certain embodiments, methods comprise administering 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 18, 24, 36, or 60 maintenance doses of the oligomeric agent, e.g., ION904. In certain embodiments, methods comprise administering a maintenance dose of the oligomeric agent, e.g., ION904, about once every 4 weeks, about once every 5 weeks, about once every 6 weeks, about once every 7 weeks, or about once every 8 weeks. In certain embodiments, methods comprise administering a first maintenance dose of the oligomeric agent, e.g., ION904, and administering a second maintenance dose about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, or about 8 weeks after administering the first maintenance dose.

[0526] In certain embodiments of the methods (and compositions for use in the methods) of administering an oligomeric agent, e.g., ION904 (e.g., a unit dose), that contains a modified oligonucleotide (e.g., comprising a nucleobase sequence consisting of 16-30 nucleosides) having a nucleobase sequence complementary to a nucleobase sequence of an equal length target region in an AGT nucleic acid, e.g., a human AGT nucleic acid such as, e.g., SEQ ID NO: 1 or 2, the first dose of oligomeric agent that is administered is a loading dose. In certain embodiments, the amount or level of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) decreases about 60%-90%, about 60%-89%, about 60%-85%, about 60%-80%, about 60%-75%, about 65%-90%, about 65%-89%, about 65%-85%, about 65%-80%, about 65%-75%, about 70%-90%, about 70%-89%, about 70%-85%, about 70%-80%, or about 70%-75% within about 2-3 weeks after administration of the loading dose compared to the amount or level of AGT RNA and/or AGT protein in the subject prior to administration of the loading dose.

[0527] In certain embodiments, one or more maintenance doses of oligomeric agent, e.g., ION904, are administered to the subject during a period of time (e.g., a maintenance period) after administration of one or more loading doses. In certain embodiments, the period of time during which one or more loading doses is/are administered and the period of time during which one or more maintenance doses is/are administered overlap. In certain embodiments, the period of time during which one or more loading doses is/are administered and the period of time during which one or more maintenance doses is/are administered do not overlap. In certain embodiments, a maintenance dose is administered after the only or last loading dose is administered. The number of

maintenance doses administered can vary depending on the desired outcome, for example, reducing the amount or level of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) or ameliorating one or more symptoms of heart failure in the subject. In certain embodiments, about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, or about 20 or more maintenance doses are administered during the period of time. In certain embodiments, the duration of the period of time is about 3 months, about 6 months, about 9 months, about 12 months, about 15 months, about 24 months, about 2 years, about 3 years, about 4 years, or about 5 years or more. In certain embodiments, the amount or level of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) decreases about 60%-90%, about 60%-89%, about 60%-85%, about 60%-80%, about 60%-75%, about 65%-90%, about 65%-89%, about 65%-85%, about 65%-80%, about 65%-75%, about 70%-90%, about 70%-89%, about 70%-85%, about 70%-80%, or about 70%-75% within about 2-3 weeks after administration of a loading dose compared to the amount or level of AGT RNA and/or AGT protein in the subject prior to administration of the loading dose. In certain embodiments, the amount or level of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) is maintained through the duration of the period of subsequently administered maintenance doses (e.g., the maintenance period) at about the same level as, or a lower level than, the level achieved about 2 weeks after administration of the loading dose(s). In certain embodiments, a method comprises administering to a subject a loading dose of about 60 mg of oligomeric agent, e.g., ION904, followed by a maintenance doses of about 60 mg each of oligomeric agent, e.g., ION904, about once every 4 weeks. In certain embodiments a method comprises administering to a subject a loading dose of about 80 mg of oligomeric agent, e.g., ION904, followed by about 5 or about 7 maintenance doses of about 80 mg each of oligomeric agent, e.g., ION904, about once every 4 weeks. In certain embodiments, a method comprises administering to a subject a loading dose of about 80 mg of oligomeric agent, e.g., ION904, followed by about 5 or about 7 maintenance doses of about 60 mg each of oligomeric agent, e.g., ION904, about once every 4 weeks.

[0528] In certain embodiments, a method comprises administering to a subject a loading dose of

about 90 mg of oligomeric agent, e.g., ION904, followed by a maintenance doses of about 90 mg each of oligomeric agent, e.g., ION904, about once every 4 weeks. In certain embodiments a method comprises administering to a subject a loading dose of about 100 mg of oligomeric agent, e.g., ION904, followed by about 5 or about 7 maintenance doses of about 100 mg each of oligomeric agent, e.g., ION904, about once every 4 weeks. In certain embodiments, a method comprises administering to a subject a loading dose of about 100 mg of oligomeric agent, e.g., ION904, followed by about 5 or about 7 maintenance doses of about 90 mg each of oligomeric agent, e.g., ION904, about once every 4 weeks.

[0529] In certain embodiments, methods comprise administering a loading dose of the oligomeric agent, e.g., ION904, once about every 2 weeks, and subsequently administering a maintenance dose of the oligomeric agent, e.g., ION904, once about every 4 weeks. In certain embodiments, methods comprise administering a loading dose once about every 4 weeks, and subsequently administering a maintenance dose once about every 4 weeks.

[0530] In certain embodiments, methods comprise administering a first maintenance dose or doses of the oligomeric agent, e.g., ION904, 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 last loading dose of the oligomeric agent, e.g., ION904.

[0531] In certain embodiments, methods comprise administering a loading dose of about 5 mg to about 120 mg of the oligomeric agent, e.g., ION904, in the same week as administering a maintenance dose of about 5 mg to about 120 mg of the oligomeric agent, e.g., ION904. In certain embodiments, the loading dose is about 5 mg, 10 mg, 20 mg, 40 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, or 120 mg of the oligomeric agent, e.g., ION904. In certain embodiments, the maintenance dose is about 5 mg, 10 mg, 20 mg, 40 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, or 120 mg of the oligomeric agent, e.g., ION904. In certain embodiments, the loading dose is about 90 mg of the oligomeric agent, e.g., ION904. In certain embodiments, a maintenance dose is about 90 mg of the oligomeric agent, e.g., ION904. In certain embodiments, a loading dose is about 100 mg of the oligomeric agent, e.g., ION904. In certain embodiments, a maintenance dose is about 100 mg of the oligomeric agent, e.g., ION904. In certain embodiments, the loading dose is administered once in the first week and the maintenance dose is administered for as long as the subject needs treatment.

[0532] 2. Dose Titration

[0533] In certain embodiments of the methods (and compositions for use in the methods) of administering an oligomeric agent, e.g., ION904 that contains a modified oligonucleotide (e.g., comprising a nucleobase sequence consisting of 16-30 nucleosides) having a nucleobase sequence complementary to a nucleobase sequence of an equal length target region in an AGT nucleic acid, e.g., a human AGT nucleic acid such as, e.g., SEQ ID NO: 1 or 2, the oligomeric agent is administered to a subject more than once (e.g., two or more times or at least two times) over a certain time period or duration of treatment (e.g., treatment period). In certain embodiments, the quantity of the oligomeric agent in each dose administered over the time period and/or the frequency of administration of the oligomeric agent over time, or for a certain time period, may be adjusted or changed depending on certain factors. For example, in certain embodiments, the quantity of the oligomeric agent, e.g., ION904, in each dose administered over time (or the frequency of administration of oligomeric agent) may be increased or decreased, for example, in response to a clinical or laboratory parameter, in order to reduce, mitigate, alleviate or prevent undesired side effects or adverse effects, or based on a subject's status. In certain embodiments of the methods (and compositions for use in the methods) of administering an oligomeric agent, e.g., ION904, the quantity, or dose, of the oligomeric agent administered to the subject at each administration is increased over time or for a certain time period. In certain embodiments of the methods (and compositions for use in the methods) of administering an oligomeric agent, e.g., ION904, the quantity of the oligomeric agent administered to the subject at each administration is decreased over time or for a certain time period.

[0534] In certain embodiments of the methods (and compositions for use in the methods) of administering an oligomeric agent, e.g., ION904, in which the oligomeric agent is administered to a subject more than once (e.g., two or more times or at least two times) over a certain time period or duration of treatment, the quantity of the oligomeric agent administered at any particular time is changed depending on the level of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein). In certain embodiments, the method includes administering a quantity (e.g., a unit dose) of the oligomeric agent, e.g., ION904, to the subject, and, after a period of time, and before administering another unit dose of the oligomeric agent, determining, or measuring, the amount of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the

blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein). If the amount of AGT RNA and/or AGT protein in the subject is less than a predetermined level, then the quantity of the oligomeric agent in the next unit dose administered to the subject is decreased (i.e., the dose of oligomeric agent is decreased) relative to the previous dose and/or the administration of the next unit dose is delayed until the amount of AGT RNA and/or AGT protein in the subject increases. If, instead, the amount of AGT RNA and/or AGT protein in the subject is greater than a predetermined level, then the quantity of the oligomeric agent in the next unit dose administered to the subject is increased (i.e., the dose of oligomeric agent is increased) relative to the previous dose and/or the administration of one or more subsequent unit doses is moved up in time or the frequency of administration of subsequent unit doses is increased at least until the amount of AGT RNA and/or AGT protein in the subject decreases.

[0535] In certain embodiments of the methods, the method includes administering a dose of an oligomeric agent, e.g., ION904 (e.g., a unit dose) that contains a modified oligonucleotide (e.g., comprising a nucleobase sequence consisting of 16-30 nucleosides) having a nucleobase sequence complementary to a nucleobase sequence of an equal length target region in an AGT nucleic acid, e.g., a human AGT nucleic acid such as, e.g., SEQ ID NO: 1 or 2, to a subject, determining or measuring the amount AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) after a period of time following the administration of the oligomeric agent, and administering a subsequent unit dose of the oligomeric agent that is a lower dose than the preceding dose of the oligomeric agent if the amount of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) is less than a predetermined level. In certain embodiments, the predetermined level is about 30%, about 29%, about 28%, about 27%, about 26%, about 25%, about 24%, about 23%, about 22%, about 21%, about 20%, about 19%, about 18%, about 17%, about 16%, about 15%, about 14%, about 13%, about 12%, about 11%, about 10%, about 9%, about 8%, about 7%, about 6%, about 5%, about 4%, about 3%, about 2% or about 1% of the amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent (e.g., the baseline level of AGT RNA and/or AGT protein in the subject). In certain embodiments, the predetermined level is about 30%, about 25%, about 20%, about 18%, about 15%, about 14%, about 13%, about 12%, about 11%, about 10%, about 9%, about 8%, about 7%, about 6%, or about 5% of

the amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent (e.g., the baseline level of AGT RNA and/or AGT protein in the subject). In certain embodiments, the predetermined level is 30%, 29%, 28%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2% or 1% of the amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent (e.g., the baseline level of AGT RNA and/or AGT protein in the subject). In certain embodiments, the predetermined level is 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, or 5% of the amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent (e.g., the baseline level of AGT RNA and/or AGT protein in the subject). In certain embodiments, the predetermined level is 15%, 14%, 13%, 12%, 11%, or 10% of the amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent (e.g., the baseline level of AGT RNA and/or AGT protein in the subject). In certain embodiments, the amount of AGT RNA and/or AGT protein is measured no earlier than 14 days, 3 days, 12 days, 11 days, 10 days, 9 days, 8 days, 7 days, 6 days, 5 days, 4 days, 3 days, 2 days or 1 day before the time of the subsequent administration of the oligomeric agent, e.g., ION904. In certain embodiments, the amount of AGT RNA and/or AGT protein is measured at least 2 weeks or at least 3 weeks after the time of the administration of the oligomeric agent, e.g., ION904, that preceded the subsequent administration of the oligomeric agent. In certain embodiments, the oligomeric agent, e.g., ION904, is administered every 4 weeks.

[0536] In certain embodiments of the methods, the method includes administering a dose of an oligomeric agent, e.g., ION904 (e.g., a unit dose amount) that contains a modified oligonucleotide (e.g., comprising a nucleobase sequence consisting of 16-30 nucleosides) having a nucleobase sequence complementary to a nucleobase sequence of an equal length target region in an AGT nucleic acid, e.g., a human AGT nucleic acid such as, e.g., SEQ ID NO: 1 or 2, to a subject, determining or measuring the amount AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) after a period of time following the administration of the oligomeric agent, and administering a subsequent dose of the oligomeric agent that is higher than the preceding dose if the amount of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) is greater than a predetermined level. In certain embodiments, the predetermined level

is about 25%, about 24%, about 23%, about 22%, about 21%, about 20%, about 19%, about 18%, about 17%, about 16%, about 15%, about 14%, about 13%, about 12%, about 11%, or about 10% of the amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent (e.g., the baseline level of AGT RNA and/or AGT protein in the subject). In certain embodiments, the predetermined level is about 20%, about 19%, about 18%, about 17%, about 16%, about 15%, about 14%, about 13%, about 12%, about 11%, or about 10%, of the amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent (e.g., the baseline level of AGT RNA and/or AGT protein in the subject). In certain embodiments, the predetermined level is about 20%, about 19%, about 18%, about 17%, about 16%, about 15%, about 14%, about 13%, or about 12%, of the amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent (e.g., the baseline level of AGT RNA and/or AGT protein in the subject). In certain embodiments, the predetermined level is 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, or 10% of the amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent (e.g., the baseline level of AGT RNA and/or AGT protein in the subject). In certain embodiments, the predetermined level is 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, or 12% of the amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent (e.g., the baseline level of AGT RNA and/or AGT protein in the subject). In certain embodiments, the predetermined level is 10%, 9%, 8%, 7%, 6%, or 5% of the amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent (e.g., the baseline level of AGT RNA and/or AGT protein in the subject). In certain embodiments, the predetermined level is 15%, 14%, 13%, 12%, or 11% of the amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent (e.g., the baseline level of AGT RNA and/or AGT protein in the subject). In certain embodiments, the amount of AGT RNA and/or AGT protein is measured no earlier than 14 days, 13 days, 12 days, 11 days, 10 days, 9 days, 8 days, 7 days, 6 days, 5 days, 4 days, 3 days, 2 days or 1 day before the time of the subsequent administration of the oligomeric agent, e.g., ION904. In certain embodiments, the amount of AGT RNA and/or AGT protein is measured at least 2 weeks or at least 3 weeks after the time of the administration of the oligomeric agent, e.g., ION904, that preceded the subsequent administration of the oligomeric agent. In certain embodiments, the oligomeric agent, e.g., ION904, is administered every 4 weeks.

[0537] In certain embodiments of the methods, a method includes administering a first quantity of

an oligomeric agent, e.g., ION904 (e.g., a unit dose) that contains a modified oligonucleotide (e.g., comprising a nucleobase sequence consisting of 16-30 nucleosides) having a nucleobase sequence complementary to a nucleobase sequence of an equal length target region in an AGT nucleic acid, e.g., a human AGT nucleic acid such as, e.g., SEQ ID NO: 1 or 2, to a subject one or more (e.g., two or more, at least two, or a plurality of) times for a first period of time followed by administering a second quantity of the oligomeric agent one or more times (e.g., two or more, at least two, or a plurality of unit doses) for a second period of time, wherein the second quantity is smaller than the first quantity (i.e., the second unit dose quantity is a lower dose than that of the first quantity). In certain embodiments, the first period of time and the second period of time do not overlap. In certain embodiments, a method comprises administering about 90 mg or 100 mg of the oligomeric agent, e.g., ION904, to a subject one or more (e.g., two or more, at least two, or a plurality of) times for a first period of time followed by administering about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, or about 90 mg of the oligomeric agent, e.g., ION904, to the subject one or more (e.g., two or more, at least two, or a plurality of) doses of for a second period of time. In certain embodiments, a method comprises administering to a subject about 90 mg or 100 mg of the oligomeric agent, e.g., ION904, once every 4 weeks for a first period of time followed by administering to the subject about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, or about 90 mg of the oligomeric agent, e.g., ION904, once every 4 weeks for a second period of time. In certain embodiments, the first period of time and the second period of time do not overlap. In a certain embodiments, the first period of time is about 9 to about 13 weeks and the second period of time is about 9 to about 13 weeks, or the first period of time is about 21 to about 25 weeks and the second period of time is about 26 to about 52 weeks or an indeterminate period of time.

[0538] V. CERTAIN THERAPIES

[0539] In certain embodiments, methods and compositions are provided for reducing the amount of AGT RNA and/or AGT protein in a subject having or at risk for heart failure (HF), such as heart failure with reduced ejection fraction (HFrEF), heart failure with preserved ejection fraction (HFpEF), heart failure with mid-range ejection fraction (HFmrEF) or heart failure with improved ejection fraction (HFimpEF). Also provided herein are methods and compositions for treating, one or more symptoms of HF in a subject having or at risk for heart failure, such as HFrEF, HFpEF, HFmrEF or HFimpEF; as well as methods and compositions for ameliorating one or more

symptoms of HF in a subject having or at risk for heart failure, such as HFrEF, HFpEF, HFmrEF or HFimpEF. In certain provided methods, the method includes administration of an oligomeric agent comprising a modified oligonucleotide having a nucleobase sequence complementary to a nucleobase sequence of an equal length target region in an angiotensinogen (AGT) nucleic acid, e.g., a human AGT nucleic acid such as, e.g., SEQ ID NO: 1 or 2. In certain embodiments, the modified oligonucleotide comprises at least 13 contiguous nucleosides at least 80%, 85%, 90%, 95% or 100% complementary to the nucleobase sequence of an equal length region of nucleobases 2046-2061 of SEQ ID NO: 1 or nucleobases 14940-14955 of SEQ ID NO: 2. In certain embodiments, the oligomeric agent comprises a cell-targeting ligand, that interacts with a receptor on the surface of a liver cell. In certain embodiments, the cell-targeting moiety contains a carbohydrate, e.g., N-acetyl galactosamine (GalNAc). In certain embodiments the method includes administering to a cell, tissue, or subject a unit dose of ION904; and in certain embodiments the composition comprises, consists essentially of or consists of a unit dose of ION904. In certain embodiments, the method includes administering a pharmaceutically acceptable carrier or excipient and the oligomeric agent, e.g., ION904. In certain embodiments, the composition comprises or consists of a pharmaceutically acceptable carrier or excipient and the oligomeric agent, e.g., ION904.

[0540] In certain embodiments of the methods and compositions for reducing the amount of AGT RNA and/or AGT protein in a subject having or at risk for heart failure, or the methods and compositions for treating, and/or ameliorating one or more symptoms of HF in, a subject having or at risk for heart failure, the heart failure is HFrEF. In certain embodiments of the methods and compositions for reducing the amount of AGT RNA and/or AGT protein in a subject having or at risk for heart failure, or the methods and compositions for treating a subject having or at risk for heart failure, the subject has a left ventricular ejection fraction of about 40%, about 35% or less, or about 30% or less. In certain embodiments of the methods and compositions for reducing the amount of AGT RNA and/or AGT protein in a subject having or at risk for heart failure, or the methods and compositions for treating a subject having or at risk for heart failure, the subject has or is at risk for HFmrEF. In certain embodiments of the methods and compositions for reducing the amount of AGT RNA and/or AGT protein in a subject having or at risk for heart failure, or the methods and compositions for treating a subject having or at risk for heart failure, the subject has a left ventricular ejection fraction of about 41% to about 49%. In certain embodiments of the methods

and compositions for reducing the amount of AGT RNA and/or AGT protein in a subject having or at risk for heart failure, or the methods and compositions for treating a subject having or at risk for heart failure, the subject has asymptomatic left ventricular dysfunction (ALVD). In certain embodiments of the methods and compositions for reducing the amount of AGT RNA and/or AGT protein in a subject having or at risk for heart failure, or the methods and compositions for treating a subject having or at risk for heart failure, the subject has structural and/or functional abnormalities of the pericardium, myocardium and/or a cardiac valve. In certain embodiments of the methods and compositions for reducing the amount of AGT RNA and/or AGT protein in a subject having or at risk for heart failure, or the methods and compositions for treating a subject having or at risk for heart failure, the subject has one or more of asymptomatic or symptomatic valvular heart disease, left ventricular hypertrophy, left ventricular fibrosis, left ventricular dilatation, and left ventricular hypocontractility. In certain embodiments of the methods and compositions for reducing the amount of AGT RNA and/or AGT protein in a subject having or at risk for heart failure, or the methods and compositions for treating a subject having or at risk for heart failure, the subject has normal blood pressure, or does not have hypertension, and/or is not being treated with an anti-hypertensive treatment.

[0541] In certain embodiments of the methods and compositions provided herein for reducing the amount of AGT RNA and/or AGT protein in a subject having or at risk for heart failure, or the methods and compositions provided herein for treating a subject having or at risk for heart failure, the amount of AGT RNA and/or AGT protein in a subject to whom (or in a cell to which) an oligomeric agent (or salt thereof) or ION904 as described herein is administered is reduced. In certain embodiments, the amount of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) is decreased by at least 70%, at least 75%, at least 80%, or at least 85% compared to the amount or level of AGT RNA and/or AGT protein prior to any administration of an oligomeric agent or ION904, or a composition containing it. In certain embodiments, the maximum decrease in the amount or level of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT protein) is less than 95%, or less than 90%, or no more than 85%, or no more than 86%, or no more than 87%, or no more than 88%, or no more than 89%, or no more than 90%, or no more than 91%, or no more than 92%, or no more than 93%, or no more than 94%, or no more than 95% compared to the

amount or level of AGT RNA and/or AGT protein prior to any administration of an oligomeric agent or ION904, or a composition containing (or consisting of a pharmaceutically acceptable carrier and) it. In certain embodiments, the amount of oligomeric agent (or salt thereof) or ION904 administered to the subject in the method is about 60 to about 120 mg, or about 75 to about 110 mg, or about 80 mg to about 110 mg, or about 90 to about 100 mg, or about 90 mg, or about 100 mg. In certain embodiments of the methods and compositions provided herein for reducing the amount of AGT RNA and/or AGT protein in a subject having or at risk for heart failure, or the methods and compositions provided herein for treating a subject having or at risk for heart failure, the oligomeric agent is ION904, or the composition contains ION904, or the method includes administering ION904 or a composition containing ION904. In certain embodiments, the composition consists of ION904 and a pharmaceutically acceptable carrier.

[0542] In certain embodiments of the methods and compositions provided herein for reducing the amount of AGT RNA and/or AGT protein in a subject having or at risk for heart failure, or the methods and compositions provided herein for treating a subject having or at risk for heart failure, the subject is, or is at risk of being, intolerant to treatment with one or more existing renin-angiotensin-aldosterone system (RAAS) inhibitor therapies, including, but not limited to, angiotensin converting enzyme (ACE) inhibitors (ACEi), angiotensin II type 1 (AT1) receptor blockers (ARB), ARB-neprilysin inhibitors (ARNi), mineralocorticoid receptor antagonists (MRA) and renin inhibitors. In certain embodiments, the subject is unable to tolerate treatment with a guideline-recommended target dose, less than a guideline-recommended initial dose, less than a guideline-recommended dose, or less than an optimal dose of a RAAS inhibitor (e.g., ACEi, ARB, ARNi, MRA). In certain embodiments, the subject has hyperkalemia, renal dysfunction, renal insufficiency (including, e.g., AKI and CKD), hypotension, and/or pulmonary disease. In certain embodiments, the subject has or is at risk of having angioedema, chronic obstructive pulmonary disease (COPD), or asthma. In certain embodiments, the subject does not have hypertension, is not being treated concurrently with an anti-hypertensive treatment, and/or is not being treated concurrently with an ACEi or ARB, or with any RAAS inhibitor. In certain embodiments, the subject is not being treated concurrently with any GDMT for heart failure. In certain embodiments, the subject is being treated with a dose and/or dosing regimen of an ACEi and/or an ARB, or any RAAS inhibitor, that is less than the guideline-recommended target dose, or less than an optimal dose of RAAS inhibitor treatment of HFrEF (e.g., a dose that is less than 60%, or less than 50%, or

less than 40% of the guideline-recommended target dose for treatment of HFrEF and/or an administration frequency or duration of treatment that is less than that a recommended administration schedule). In certain embodiments, the subject is not being treated concurrently with a neprilysin inhibitor. In certain embodiments, the subject has been previously treated with but is no longer being treated with a GDMT for heart failure. In certain embodiments, the subject has been previously treated with but is no longer being treated with a RAAS inhibitor. In certain embodiments, the subject has been previously treated with but is no longer being treated with and ACEi, ARB, ARNi, or MRA. In certain embodiments of the methods for reducing the amount of AGT RNA and/or AGT protein in a subject having or at risk for heart failure, or the methods for treating a subject having or at risk for heart failure, that include administration of an oligomeric agent or ION904 as described herein, the method is effective in treating, or ameliorating one or more symptoms of, heart failure, e.g., HFrEF, without causing hypotension, or at risk for heart failure (such as HFrEF), or does not significantly alter (e.g., increase) potassium levels (e.g., blood, serum, or plasma potassium levels) in a subject having, or at risk for heart failure (such as HFrEF), or does not significantly alter bradykinin homeostasis or increase bradykinin levels (e.g., blood, serum, or plasma bradykinin levels) in a subject having, or at risk for heart failure (such as HFrEF).

[0543] In certain embodiments of the methods and compositions for reducing the amount or level of AGT RNA and/or AGT protein in a subject having, or at risk for, heart failure, or the methods and compositions for treating a subject having, or at risk for, heart failure, in which the method includes administration of (or the composition contains, consists essentially of, or consists of) an oligomeric agent (or salt thereof) or ION904 as described herein, administration of the oligomeric agent or ION904 improves cardiac function, reduces cardiac dilation, reduces cardiac fibrosis, reverses or attenuates cardiac remodeling, and/or increases LVEF in the subject. In certain embodiments, administration of the oligomeric agent or ION904 improves left ventricular end diastolic volume (LVEDV), improves LV strain, improves a 6-minute walk test, and/or improves quality of life as assessed by patient reported outcomes of a subject having, or at risk for, heart failure. In certain embodiments, administration of the oligomeric agent or ION904 improves ESVi or LVESV of the subject. In certain embodiments, the level of N-terminal prohormone B-type natriuretic peptide (NT-proBNP), B-type natriuretic peptide (BNP), high-sensitive cardiac troponin T (hs-cTnT), and/or cardiac troponin T (cTnT) in blood, plasma or serum, of a subject to whom the oligomeric agent or

ION904, or a composition containing the oligomeric agent or ION904, is administered decreases compared to the baseline level prior to any administration of the oligomeric agent or ION904.

[0544] In certain embodiments of the methods provided herein for reducing the amount of AGT RNA and/or AGT protein in a subject having or at risk for heart failure, or the methods provided herein for treating, and/or ameliorating one or more symptoms of heart failure in, a subject having or at risk for heart failure, the method includes administering an oligomeric agent (or salt thereof) or ION904 as described herein and no other active agent for the treatment of heart failure and/or suppression or inhibition of the RAAS is administered to the subject for the duration of the oligomeric agent treatment period. In certain embodiments of the methods provided herein for reducing the amount of AGT RNA and/or AGT protein in a subject having or at risk for heart failure, or the methods provided herein for treating, and/or ameliorating one or more symptoms of heart failure in, a subject having or at risk for heart failure, the method includes administering an oligomeric agent (or salt thereof) or ION904 as described herein and administering active agent. In certain embodiments, the method includes administering an oligomeric agent or ION904 as described herein and administering a GDMT for heart failure, e.g., HFrEF. In certain embodiments, the GDMT for heart failure is one or more of an ACEi, ARB, ARNi, MRA, beta blocker and SGLT2. In certain embodiments, the dose of the GDMT for heart failure is the Guideline-recommended initial dose or target dose. In certain embodiments, the method includes administering the oligomeric agent or ION904 to the subject and administering a dose of an ACEi, ARB, ARNi and/or an MRA that is less than the Guideline-recommended dose (or dose recognized by the medical community as therapeutic, efficacious, optimal, or fully or maximally efficacious) and/or dosing regimen for treatment of heart failure, e.g., HFrEF (e.g., a dose that is less than 60%, or less than 50%, or less than 40% of the Guideline-recommended dose and/or optimal dose for treatment of HFrEF and/or an administration frequency or duration of treatment that is less than the Guideline-recommended dose or optimal administration frequency or treatment period. In certain embodiments, the method includes administering an oligomeric agent or ION904 as described herein and administering a neprilysin inhibitor. In certain embodiments the neprilysin inhibitor is sacubitril or a modified oligonucleotide (such as, for example, a single-stranded modified oligonucleotide) having a nucleobase sequence complementary to a sequence in a neprilysin nucleic acid (e.g., a modified antisense oligonucleotide targeting a human neprilysin (MME) RNA).

[0545] In certain embodiments of the methods and compositions for administering an oligomeric agent or ION904 provided herein, or the methods and compositions for reducing the amount or level of AGT RNA and/or AGT protein in a subject having, or at risk for, heart failure, or the methods and compositions for treating a subject having, or at risk for, heart failure, the method includes administering (or the composition contains, consists essentially of, or consists of) a quantity (or a dose, fixed dose, a unit dose) of the oligomeric agent (or salt thereof) or ION904 within the range of about 5 mg to about 200 mg. In certain embodiments, the amount of oligomeric agent or ION904, is or is about 60 mg, or is or is about 65 mg, or is or is about 70 mg, or is or is about 75 mg, or is or is about 80 mg, or is or is about 85 mg, or is or is about 90 mg, or is or is about 95 mg, or is or is about 100 mg, or is or is about 105 mg, or is or is about 110 mg, or is or is about 115 mg, or is or is about 120 mg. In certain embodiments, the quantity of oligomeric agent (or salt thereof) or ION904 is in a pharmaceutical composition. In certain embodiments, the pharmaceutical composition contains a pharmaceutically acceptable carrier or excipient. In certain embodiments, a composition contains, or consists of a pharmaceutically acceptable carrier and, 90 mg or 100 mg of the oligomeric agent or ION904. In certain embodiments, the quantity of oligomeric agent (or salt thereof) or ION904 is in a unit dose form. In certain embodiments, the unit dose contains, or consists of a pharmaceutically acceptable carrier and, 50-120 mg, or 60-120 mg, or 70-110 mg, or 80-100 mg, or 90-100 mg of the oligomeric agent or ION904, or 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, or 120 mg of the oligomeric agent or ION904. In certain embodiments, the unit dose is formulated for parenteral administration, e.g., subcutaneous administration, to a subject, such as a subject having or at risk for heart failure, such as HFrEF. In certain embodiments, a composition contains an oligomeric agent (or salt thereof) or ION904 and another active agent. In certain embodiments, the composition contains a neprilysin inhibitor. In certain embodiments, the neprilysin inhibitor is sacubitril. In certain embodiments of the methods and compositions, the amount of the oligomeric agent (or salt thereof) or ION904 administered in the method, or contained in the composition, is effective in treating, or ameliorating one or more symptoms of, heart failure, e.g., HFrEF, but does not significantly alter (e.g., decrease) systemic (e.g., systolic and/or diastolic) blood pressure in a subject having, or at risk for heart failure (such as HFrEF), or does not significantly alter (e.g., increase) potassium levels (e.g., blood, serum, or plasma potassium levels) in a subject having, or at risk for heart failure (such as HFrEF), or but does

not significantly alter bradykinin homeostasis or increase bradykinin levels (e.g., blood, serum, or plasma bradykinin levels) in a subject having, or at risk for heart failure (such as HFrEF).

[0546] In certain embodiments of the methods for administering an oligomeric agent (or salt thereof) or ION904 provided herein, or the methods for reducing the amount or level of AGT RNA and/or AGT protein in a subject having, or at risk for, heart failure, or the methods for treating a subject having, or at risk for, heart failure, the oligomeric agent (or salt thereof) or ION904, or composition containing it, is administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 times or more. In certain embodiments, the oligomeric agent (or salt thereof) or ION904, or composition containing it, is administered once every 84 days, once every 56 days, once every 30 days, once every 28 days, once every 20 days, once every 10 days, once every 7 days, once every 6 days, once every 5 days, once every 4 days, once every 3 days, once every 2 days, once every other day, or once each day. In certain embodiments, the oligomeric agent or ION904, or composition containing it, is administered once every 3 weeks, once every 4 weeks, once every 5 weeks, once every 6 weeks, once every 7 weeks, once every 8 weeks, once every 9 weeks, once every 10 weeks, once every 11 weeks, or once every 12 weeks. In certain embodiments, the oligomeric agent (or salt thereof) or ION904 is administered over a period of about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, about 21 weeks, about 22 weeks, about 23 weeks, about 24 weeks, about 25 weeks, about 26 weeks, about 27 weeks, about 28 weeks, or more. In certain embodiments, the oligomeric agent (or salt thereof) or ION904, or composition containing it, is administered about once every 4 weeks for at least about 13 weeks, at least about 17 weeks, at least about 21 weeks, at least about 25 weeks, at least about 26 weeks, at least about 27 weeks, at least about 29 weeks, at least about 33 weeks, at least about 37 weeks, at least about 41 weeks, at least about 45 weeks, at least about 49 weeks, at least about 52 weeks, or at least about 53 weeks. In certain embodiments, the oligomeric agent (or salt thereof) or ION904, or composition containing it, can be administered by a syringe. In certain embodiments, the oligomeric agent (or salt thereof) or ION904, or composition containing it, can be administered subcutaneously.

[0547] In certain embodiments of the methods for administering an oligomeric agent (or salt thereof) or ION904 provided herein, or the methods for reducing the amount or level of AGT RNA and/or AGT protein in a subject having, or at risk for, heart failure, or the methods for treating a subject having, or at risk for, heart failure, the method includes administering a quantity (e.g., dose, unit dose) of the oligomeric agent or ION904, to a subject, and, after a period of time, and before

administering another unit dose or quantity of the oligomeric agent, determining, or measuring, the amount of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein). If the amount of AGT RNA and/or AGT protein in the subject is less than a predetermined level, then the quantity of the oligomeric agent or ION904 in the next unit dose administered to the subject is decreased (i.e., the dose of oligomeric agent is decreased) relative to the previous dose and/or the administration of the next unit dose is delayed until the amount of AGT RNA and/or AGT protein in the subject increases. If, instead, the amount of AGT RNA and/or AGT protein in the subject is greater than a predetermined level, then the quantity of the oligomeric agent or ION904 in the next unit dose administered to the subject is increased (i.e., the dose of oligomeric agent is increased) relative to the previous dose and/or the administration of one or more subsequent unit doses is moved up in time or the frequency of administration of subsequent unit doses is increased at least until the amount of AGT RNA and/or AGT protein in the subject decreases.

[0548] In certain embodiments of the methods and compositions provided herein methods include administering (or the composition contains, consists essentially of, or consists of) an oligomeric agent containing an oligonucleotide (e.g., a modified oligonucleotide) having a nucleobase sequence complementary to a nucleobase sequence of an equal length target region in an AGT nucleic acid, having at least 13 contiguous nucleosides at least 80%, 85%, 90%, or 95% complementary to the nucleobase sequence of an equal region of nucleobases 2046-2061 of SEQ ID NO: 1 or nucleobases 14940-14955 of SEQ ID NO: 2. In certain embodiments, the nucleobase sequence comprises at least 13, at least 14, at least 15 or at least 16 contiguous nucleobases complementary to an equal length region of nucleobases 2046-2061 of SEQ ID NO: 1 or nucleobases 14940-14955 of SEQ ID NO: 2. In certain embodiments, the nucleobase sequence contains least 12, at least 13, at least 14, at least 15 or at least 16 contiguous nucleobases of SEQ ID NO: 3. In certain embodiments, the oligonucleotide (e.g., modified oligonucleotide) consists of the nucleobase sequence of SEQ ID NO: 3. In certain embodiments, the oligonucleotide is a modified oligonucleotide containing at least one, at least two, at least three, at least four, at least 5 or at least 6 modified nucleosides containing a modified sugar moiety, or has 1 to 6 modified nucleosides containing a modified sugar moiety. In certain embodiments, each modified sugar moiety is independently selected from a 2'-MOE sugar moiety and a bicyclic sugar moiety (e.g., cET sugar moiety). In certain embodiments, at least one, or at least two, or at least three of the nucleosides contains a cEt sugar moiety, or 1-3 of the nucleosides

contains a cEt sugar moiety. In certain embodiments in which the modified oligonucleotide contains at least 1, at least 2, at least 3, at least 4, at least 5 or at least 6 modified nucleosides containing a modified sugar moiety, the remainder of the nucleosides in the modified oligonucleotide are DNA nucleosides. In certain embodiments, the modified includes a deoxy region. In certain embodiments, each nucleoside of the deoxy region is a 2'-deoxynucleoside, e.g., a DNA nucleoside. In certain embodiments, the deoxy region is flanked on the 5'-side by a 5'-region consisting of linked 5'-region nucleosides and on the 3'-side by a 3'-region consisting of linked 3'-region nucleosides; wherein the 3'-most nucleoside of the 5'-region contains a modified sugar moiety and the 5'-most nucleoside of the 3'-region contains a modified sugar moiety. The three regions (the 5'-region, the deoxy region, and the 3'-region) form a contiguous sequence of nucleosides. In certain embodiments, each nucleoside of the 5'-region and each nucleoside of the 3'-region contains a modified sugar moiety. In certain embodiments, each internucleoside linkage between adjacent nucleosides in the deoxy region is a phosphorothioate internucleoside linkage and the internucleoside linkages between nucleosides of the 5'-region, nucleosides of the 3'-region, and between the 3'-most nucleoside of the 5'-region and the 5'-most nucleoside of the deoxy region, and between the 5'-most nucleoside of the 3'-region and the 3'-most nucleoside of the deoxy region are each independently a phosphorothioate internucleoside linkage or a phosphodiester internucleoside linkage.

[0549] In certain embodiments of the methods (and compositions for use in the methods) of administering an oligomeric agent, e.g., ION904 (e.g., a unit dose) that contains a modified oligonucleotide (e.g., comprising a nucleobase sequence consisting of 16-30 nucleosides) having a nucleobase sequence complementary to a nucleobase sequence of an equal length target region in an AGT nucleic acid, e.g., a human AGT nucleic acid such as, e.g., SEQ ID NO: 1 or 2, to a subject, no other active agent for the treatment of heart failure and/or suppression or inhibition of the RAAS is administered to the subject for the duration of the oligomeric agent treatment period. In certain embodiments, no other active agent for the treatment of heart failure and/or suppression or inhibition of the RAAS is administered to the subject simultaneously (i.e., within the same 24-hr period of administration of the oligomeric agent, e.g., ION904. In certain embodiments of the methods, the oligomeric agent, e.g., ION904, is administered as a monotherapy for reducing AGT RNA and AGT protein levels, suppression or inhibition of the RAAS and/or treatment of heart failure. In certain embodiments of the methods, the subject is not being treated concurrently with an anti-hypertensive treatment, and/or is not being treated concurrently with an ACEi or ARB, or with any RAAS

inhibitor. Antihypertensive treatments include, for example, thiazide-type diuretics, calcium channel blockers, ACEi, ARB, beta blockers, alpha-1 blocker, centrally acting sympatholytic agents, and direct acting vasodilators (e.g., hydralazine). In certain embodiments, the subject is not being treated concurrently with any GDMT for heart failure, e.g., HFrEF.

[0550] In certain embodiments of the methods (and compositions for use in the methods) of administering an oligomeric agent, e.g., ION904 (e.g., a unit dose) that contains a modified oligonucleotide (e.g., comprising a nucleobase sequence consisting of 16-30 nucleosides) having a nucleobase sequence complementary to a nucleobase sequence of an equal length target region in an AGT nucleic acid, e.g., a human AGT nucleic acid such as, e.g., SEQ ID NO: 1 or 2, the method includes administering to the subject the oligomeric agent and administering to the subject a GDMT for heart failure, e.g., HFrEF. In certain embodiments, the GDMT for heart failure is one or more of an ACEi, ARB, ARNi, MRA, beta blocker and SGLT2. In certain embodiments, the method includes administering the oligomeric agent, e.g., ION904, to the subject and administering a dose of an ACEi, ARB, ARNi and/or an MRA that is less than the guideline-recommended dose (or dose recognized by the medical community as therapeutic, efficacious, optimal, or fully or maximally efficacious) and/or dosing regimen for treatment of heart failure, e.g., HFrEF (e.g., a dose that is less than 60%, or less than 50%, or less than 40% of the guideline-recommended dose and/or optimal dose for treatment of HFrEF and/or an administration frequency or duration of treatment that is less than the guideline-recommended dose or optimal administration frequency or treatment period. In certain embodiments, the method includes administering the oligomeric agent, e.g., ION904, to the subject and administering to the subject a neprilysin inhibitor. In certain embodiments, the subject is being treated concurrently with a neprilysin inhibitor and is not being treated concurrently with an ACEi or ARB, or with any other RAAS inhibitor. In certain embodiments, the method includes administering the oligomeric agent, e.g., ION904, to the subject and administering a neprilysin inhibitor to the subject wherein the subject is not being treated concurrently with any other GDMT for heart failure.

[0551] In certain embodiments of the methods (and compositions for use in the methods) of administering an oligomeric agent, e.g., ION904 (e.g., a unit dose) that contains a modified oligonucleotide (e.g., comprising a nucleobase sequence consisting of 16-30 nucleosides) having a nucleobase sequence complementary to a nucleobase sequence of an equal length target region in an AGT nucleic acid, e.g., a human AGT nucleic acid such as, e.g., SEQ ID NO: 1 or 2, the method

includes concurrently administering the oligomeric agent, e.g., ION904, and at least one other active agent. In certain embodiments, the at least one other active agent treats heart failure, e.g., HFrEF, HFmrEF or HFpEF, or a symptom thereof. In certain embodiments, the at least one other active agent treats HFrEF, or a symptom thereof. In certain embodiments, the oligomeric agent, e.g., ION904, is administered concurrently with the at least one other active agent to produce a combinational effect. In certain embodiments, the oligomeric agent, e.g., ION904, is administered concurrently with the at least one other active agent to produce a synergistic effect. Concurrent administration of an oligomeric agent, e.g., ION904, and at least one other active agent means the oligomeric agent, e.g., ION904, is administered and at least one other active agent is also administered to the subject. In certain embodiments, at least a period of time during the total treatment time period (duration) comprises concurrent administration. In certain embodiments, concurrent administration of at least one other active agent spans the total treatment time period of the oligomeric agent, e.g., ION904. In certain embodiments, concurrent administration with at least one other active agent comprises at least one other active agent that is the same throughout concurrent administration. In certain embodiments, concurrent administration with at least one other active agent comprises at least one other active agent that change over concurrent administration.

[0552] In certain embodiments of concurrent administration, the oligomeric agent, e.g., ION904, and the at least one other active agent are administered simultaneously (i.e., within the same 24-hour period). In certain embodiments, the oligomeric agent, e.g., ION904, and the at least one other active agent may be contained together in a single formulation or composition, or may be separate compositions. In certain embodiments of concurrent administration, the oligomeric agent, e.g., ION904, and the at least one other active agent are administered sequentially (i.e., a first administration followed by a second administration). In certain embodiments administration is minutes apart. In some embodiments, administration is hours apart. In some embodiments administration is 1, 2, 3, 4, or 5 hours apart. In some embodiments, administration is half a day or a day apart.

[0553] In certain embodiments, an active agent that may be administered concurrently with the oligomeric agent, e.g., ION904, is an ACE inhibitor (e.g., lisinopril, ramipril, perindopril, enalapril, benazepril, quinapril, captopril, fosinopril, trandolapril, moexipril, enalaprilat, trandolapril), an ARB (e.g., losartan, olmesartan, valsartan, candesartan, irbesartan, telmisartan, azilsartan, eprosartan), a

beta blocker (e.g., bisoprolol, carvedilol, carvedilol CR, metoprolol), a calcium channel blocker, a loopdiuretic, an alpha-1 blocker, centrally acting sympatholytic agent, SGLT2 inhibitor (SGLT2i, e.g., empagliflozin, canagliflozin, dapagliflozin, ertugliflozin), a direct acting vasodilator (e.g. hydralazine), or a neprilysin inhibitor (e.g., sacubitril), or combination of any of the agents.

[0554] In certain embodiments of the methods (and compositions for use in the methods) of administering an oligomeric agent, e.g., ION904 (e.g., a unit dose) that contains a modified oligonucleotide (e.g., comprising a nucleobase sequence consisting of 16-30 nucleosides) having a nucleobase sequence complementary to a nucleobase sequence of an equal length target region in an AGT nucleic acid, e.g., a human AGT nucleic acid such as, e.g., SEQ ID NO: 1 or 2, the method includes administering the oligomeric agent, e.g., ION904, and administering a neprilysin inhibitor. In certain embodiments the neprilysin inhibitor is sacubitril (e.g., about 40 to about 100 mg) or a modified oligonucleotide (such as, for example, a single-stranded modified oligonucleotide) having a nucleobase sequence complementary to a sequence in a neprilysin nucleic acid (e.g., a modified antisense oligonucleotide targeting a human neprilysin (MME) RNA). In certain embodiments, the oligomeric agent, e.g., ION904, and the neprilysin inhibitor are administered simultaneously (i.e., within the same 24-hour period). In certain embodiments, the oligomeric agent, e.g., ION904, and the neprilysin inhibitor are administered sequentially (i.e., more than 24 hours apart). In certain embodiments, the oligomeric agent, e.g., ION904, and the neprilysin inhibitor are administered in a single composition containing both molecules. In certain embodiments, the oligomeric agent, e.g., ION904, and the neprilysin inhibitor are administered in separate compositions.

[0555] A. Methods

[0556] In certain embodiments, provided are methods that include administering an oligomeric agent to a cell or subject. Also provided herein are methods for reducing the amount of AGT RNA and/or AGT protein in a cell or subject. Further provided herein are methods for reducing the amount of AGT RNA and/or AGT protein in a subject having or at risk for heart failure, such as HFrEF, HFpEF, HFimpEF, or HFmrEF. Also provided are methods for treating a subject having or at risk for heart failure, such as HFrEF, HFpEF, HFimpEF, or HFmrEF, or for ameliorating one or more symptoms of heart failure, e.g., HFrEF, HFpEF, HFimpEF, or HFmrEF. In certain embodiments, provided herein are methods for reducing the amount of AGT RNA and/or AGT protein in a subject having or at risk for HFrEF, and methods for treating a subject having or at risk for HFrEF and/or or for ameliorating one or more symptoms of HFrEF.

[0557] In certain embodiments of any of the methods, the method includes administering an oligomeric agent, or salt thereof (e.g., a unit dose), e.g., ION904, that contains an oligonucleotide (e.g., comprising a nucleobase sequence consisting of 16-30 nucleosides), e.g., a modified oligonucleotide, having a nucleobase sequence complementary to a nucleobase sequence of an equal length target region in an AGT nucleic acid, e.g., a human AGT nucleic acid such as, e.g., SEQ ID NO: 1 or 2, to a cell or subject. In certain embodiments, the oligomeric agent is any one of such oligomeric agents described herein and/or containing any of the oligonucleotides described herein. In certain embodiments, the oligonucleotide, e.g., modified oligonucleotide, of the oligomeric agent comprises or consists of a nucleobase sequence that is at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% complementary to a region of SEQ ID NOs: 1 or 2. In certain embodiments, the oligonucleotide of the oligomeric agent is any one of such oligonucleotides, e.g., modified oligonucleotides, described herein. In certain embodiments, the nucleobase sequence of the modified oligonucleotide, is 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23 contiguous nucleosides in length. In certain embodiments, the oligomeric agent comprises or consists of a modified oligonucleotide, containing a nucleobase sequence complementary to an equal length region of nucleobases 2046-2061 of SEQ ID NO: 1 or nucleobases 14940-14955 of SEQ ID NO: 2. In certain embodiments, the oligomeric agent contains a conjugate group. In certain embodiments, the oligomeric agent consists of a modified oligonucleotide, containing a nucleobase sequence complementary to an equal length region of nucleobases 2046-2061 of SEQ ID NO: 1 or nucleobases 14940-14955 of SEQ ID NO: 2 attached to a conjugate group. In certain embodiments, the conjugate group contains a cell-targeting moiety that interacts with or binds to a cell surface protein of a hepatic cell. In certain embodiments, the oligonucleotide is attached to a conjugate group containing one or more GalNAc moieties, e.g., tris(hexamethylamino)-C6 GalNAc₃. In certain embodiments, the conjugate group is attached to a terminus of the oligonucleotide, e.g., the 5' terminal nucleobase of the oligonucleotide. In certain embodiments, the nucleobase sequence of the modified oligonucleotide of the oligomeric agent includes at least 12, at least 13, at least 14, at least 15, or at least 16 contiguous nucleobases complementary to an equal length region of nucleobases 2046-2061 of SEQ ID NO: 1 (GENBANK Accession No. NM_000029.3). In certain embodiments, the nucleobase sequence of the modified oligonucleotide includes at least 12, at least 13, at least 14, at least 15, or at least 16 contiguous nucleobases of SEQ ID NO: 3. In certain embodiments, the modified oligonucleotide of the oligomeric agent consists of SEQ ID NO: 3. In certain

embodiments, the oligomeric agent consists of a modified oligonucleotide, having a nucleobase sequence of SEQ ID NOs: 3, 4 or 5 attached to a conjugate group. In certain embodiments, the oligomeric agent is ION904 (represented in certain embodiments by Structure 1), including any salt (e.g., pharmaceutically acceptable salt) of ION904, e.g., potassium, calcium, magnesium, and sodium salts (see, e.g., Structure 2), ester of ION904, or salts of such esters.

[0558] In certain embodiments of the methods that include administering to a subject an oligomeric agent (or salt thereof), e.g., ION904, the subject is one having, or at risk for, heart failure. Subjects having heart failure have a structural or functional impairment of ventricular filling or ejection of blood and have signs or symptoms associated with the structural and/or functional impairment. Structural impairments (e.g., structural heart disease) include, for example, LV chamber dilation, ventricular hypertrophy, LV wall thickness ≥ 12 mm, wall motion abnormalities, and valvular heart disease. Functional impairments include, for example, reduced ventricular systolic function, reduced ejection fraction, reduced ($<16\%$) global longitudinal strain, increased filling pressure, and valve regurgitation. Signs and symptoms of heart failure include elevated BNP (e.g., ≥ 35 pg/ml), elevated NT-proBNP (e.g., ≥ 125 pg/ml), rapid or irregular heartbeat, palpitation, shortness of breath, chest pain, dizziness, weakness, dyspnea, orthopnea, edema, hepatic congestion, and ascites. Asymptomatic subjects having structural or functional heart disease (e.g., asymptomatic left ventricular dysfunction (ALVD)) or cardiomyopathies are considered to be at risk for heart failure. Risk factors for development of heart failure include diabetes, prediabetes, atherosclerotic cardiovascular disease (CVD), obesity, and hypertension. Causes of heart failure include ischemic heart disease, myocardial infarction, genetic cardiomyopathies, amyloidosis, tachycardia, hypertension and valvular heart disease.

[0559] In certain embodiments of the methods that include administering to a subject an oligomeric agent (or salt thereof), e.g., ION904, the subject to whom the oligomeric agent is administered is one having, or at risk for, HFrEF, HFmrEF, HFimpEF or HFpEF. Left ventricular ejection fraction (LVEF) values used for classification of heart failure in the GDMT are: HFrEF = LVEF $\leq 40\%$; HFmrEF = LVEF 41%-49%; HFpEF = LVEF $\geq 50\%$; and HFimpEF (referred to as a subgroup of HFrEF) = previous LVEF $\leq 40\%$ and a follow-up measurement of LVEF $>40\%$ (Heidenreich et al (2022) *Circulation* 145(18):e895-e1032, 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines). The GDMT also include additional criteria for

diagnosis of HFmrEF and HFpEF which are evidence of increased LV filling pressures (e.g., elevated levels of natriuretic peptides, echocardiographic diastolic parameters, invasive hemodynamic measurements and structural alterations, such as an increase in left atrial size and volume (left atrial volume index) and/or an increase in LV mass (LV mass index)). In certain embodiments of the methods provided herein that include administering an oligomeric agent, e.g., ION904, to a subject having, or at risk for, heart failure, the subject has an LVEF of greater than about 50%, or about 50% or less, about 40% or less, or about 35% or less, or about 30% or less. In certain embodiments, the subject has an LVEF of about 40% or less. In certain embodiments, the subject has an LVEF of about 35% or less. In certain embodiments, the subject has an LVEF of about 41%-49%. In certain embodiments, the subject has an LVEF greater than 40% but previously had an LVEF of about 40% or less. In certain embodiments, the subject has an LVEF greater than 40% but previously had an LVEF of about 40% or less and has an at least 10-point increase in LVEF from baseline LVEF. In certain embodiments, the subject has an LVEF of greater than about 50% and has an elevated left ventricle (LV) filling pressure, elevated left atrial size and/or volume and/or an elevated LV mass.

[0560] In certain embodiments, methods include administering to a subject an oligomeric agent (or salt thereof), e.g., ION904, wherein a subject has, or is at risk for, heart failure, and has asymptomatic left ventricular dysfunction (ALVD). In certain embodiments, a subject has, or is at risk for, heart failure, and has structural and/or functional abnormalities of the pericardium, myocardium and/or a cardiac valve. In certain embodiments of the methods, a subject has, or is at risk for, heart failure, and has one or more of asymptomatic or symptomatic valvular heart disease, left ventricular hypertrophy, left ventricular fibrosis, left ventricular dilatation, and left ventricular hypocontractility.

[0561] In certain embodiments of methods provided herein that include administering to a subject an oligomeric agent (or salt thereof), e.g., ION904, a subject has, or is at risk for, heart failure, and has normal systemic blood pressure (e.g., normotension) or does not have hypertension. In certain embodiments, normal systolic blood pressure is within the range of about 90 mm Hg to about 120 mm Hg, about 90 mm Hg to about 125 mm Hg, about 100 mm Hg to about 120 mm Hg, or about 100 mm Hg to about 125 mm Hg, and normal diastolic blood pressure is within the range of about 60 mm Hg and about 80 mm Hg. In certain embodiments, a subject has, or is at risk for, heart failure, and has elevated systemic blood pressure or high systemic blood pressure (e.g.,

hypertension). In certain embodiments, elevated systolic blood pressure is about 125 mm Hg to about 129 mm Hg and high systolic blood pressure (i.e., hypertension) is about 130 mm Hg or higher.

[0562] In certain embodiments of methods provided herein that include administering to a subject an oligomeric agent (or salt thereof), e.g., ION904, a subject has, or is at risk for, heart failure, and is, or is at risk of being, intolerant to treatment with a renin-angiotensin-aldosterone system (RAAS) inhibitor. Examples of RAAS inhibitors include ACEi, ARB, ARNi, renin inhibitors and MRA. Such subjects have an inability to tolerate or have a diminished tolerance to certain effects (e.g., adverse or side effects) that may occur with inhibition or suppression of the RAAS and/or treatment with a RAAS inhibitor, particularly treatment with a therapeutically effective, efficacious, optimal or Guideline-recommended dose of a RAAS inhibitor for a given indication, e.g., heart failure, such as e.g., HFrEF. For example, in some RAAS inhibitor intolerant subjects, treatment with a RAAS inhibitor is associated with adverse effects such as cough, hypotension or hypotensive symptoms, hyperkalemia, renal dysfunction and angioedema. In some cases, the extent or severity of the adverse effect is such that RAAS inhibitor treatment is either discontinued, switched, or continued at doses and/or dosing regimens that are lower and/or have a decreased frequency of administration than that recommended in GDMT and/or recognized as therapeutic, efficacious, optimal, or fully or maximally efficacious. Thus, many RAAS inhibitor intolerant subjects are suboptimally dosed (e.g., taking no RAAS inhibitor or less than a Guideline-recommended target dose, such as less than about 80%, 70%, 60%, 55%, 50%, 45%, or 40% of such a recommended dose).

[0563] In certain embodiments of methods provided herein that include administering to a subject an oligomeric agent (or salt thereof), e.g., ION904, a subject has, or is at risk for, heart failure, and is being treated with a RAAS inhibitor. In certain embodiments, the RAAS inhibitor is one or more of an ACEi, ARB, ARNi, renin inhibitor and MRA. In certain embodiments, the RAAS inhibitor is one or more of an ACEi, ARB, ARNi, and MRA. In certain embodiments, the subject is being treated with a dose of RAAS inhibitor that is less than the Guideline-recommended target dose for treatment of HF, e.g., HFrEF, and/or is being treated with the RAAS inhibitor less frequently or for a shorter duration than the Guideline-recommended dosing frequency or duration. In certain embodiments, the dose of the RAAS inhibitor (e.g., ACE inhibitor, ARB, ARNi, MRA or renin inhibitor) is less than about 80%, 70%, 60%, 55%, 50%, 45%, or 40% of the Guideline-recommended dose for treatment of HF, e.g., HFrEF. In certain embodiments of methods provided herein that include

administering to a subject an oligomeric agent, e.g., ION904, a subject has, or is at risk for, heart failure, and has been previously treated with a RAAS inhibitor but is no longer being treated with a RAAS inhibitor. In certain embodiments, the RAAS inhibitor is one or more of an ACEi, ARB, ARNi, renin inhibitor and MRA. In certain embodiments, the RAAS inhibitor is one or more of an ACEi, ARB, ARNi, and MRA. In certain embodiments, the subject was treated with a dose of RAAS inhibitor that is less than the Guideline-recommended dose for treatment of HF, e.g., HFrEF, and/or was treated with the RAAS inhibitor less frequently or for a shorter duration than the Guideline-recommended dosing frequency or duration. In certain embodiments, the dose of the RAAS inhibitor (e.g., ACE inhibitor, ARB, ARNi, MRA or renin inhibitor) was less than about 80%, 70%, 60%, 55%, 50%, 45%, or 40% of the Guideline-recommended dose for treatment of HF, e.g., HFrEF. In certain embodiments of methods provided herein that include administering an oligomeric agent, e.g., ION904, to a subject having, or at risk for, heart failure, the subject is not being treated concurrently with a RAAS inhibitor. In certain embodiments of methods provided herein that include administering an oligomeric agent, e.g., ION904, to a subject having, or at risk for, heart failure, the subject is not being treated concurrently with an ACE inhibitor, an ARB, an ARNi, a MRA or a renin inhibitor. In certain embodiments of methods provided herein that include administering an oligomeric agent, e.g., ION904, to a subject having, or at risk for, heart failure, the subject is not being treated concurrently with any guideline-directed medical therapy (GDMT) for heart failure. In certain embodiments of methods provided herein that include administering an oligomeric agent, e.g., ION904, to a subject having, or at risk for, heart failure, the subject is not being treated concurrently with any guideline-directed medical therapy (GDMT) for HFrEF. In certain embodiments of methods provided herein that include administering an oligomeric agent, e.g., ION904, to a subject having, or at risk for, heart failure, the subject has been previously treated with but is no longer being treated with a GDMT for heart failure. In certain embodiments of methods provided herein that include administering an oligomeric agent, e.g., ION904, to a subject having, or at risk for, heart failure, the subject has been previously treated with but is no longer being treated with a GDMT for HFrEF.

[0564] In certain embodiments, a subject having or at risk for heart failure who may benefit from RAAS inhibitor therapy has a greater risk for, susceptibility to, or sensitivity to, potential adverse effects of a RAAS inhibitor or RAAS inhibitor treatment. Such subjects include, for example, those who have normal-to-low systemic blood pressure, hypotension, hyperkalemia, renal dysfunction,

renal insufficiency (including, e.g., AKI and CKD), angioedema or history of angioedema, and/or pulmonary disease, e.g., asthma or COPD. Such subjects have conditions that could be exacerbated by effects of RAAS inhibitors.

[0565] In certain embodiments of methods provided herein that include administering to a subject an oligomeric agent (or salt thereof), e.g., ION904, a subject has, or is at risk for, heart failure, and has a systolic blood pressure less than about 130 mm Hg, or less than about 125 mm Hg, or less than about 120 mm Hg, or less than about 110 mm Hg, or within the range of about 90 mm Hg to about 130 mm Hg, or about 100 mm Hg to about 130 mm Hg, or about 110 mm Hg to about 130 mm Hg, or about 90 mm Hg to about 125 mm Hg, or about 100 mm Hg to about 125 mm Hg, or about 110 mm Hg to about 125 mm Hg, or about 90 mm Hg to about 120 mm Hg, or about 100 mm Hg to about 120 mm Hg, or about 110 mm Hg to about 120 mm Hg, or about 90 mm Hg to about 110 mm Hg or about 90 mm Hg to about 100 mm Hg. In certain embodiments of methods provided herein that include administering to a subject an oligomeric agent, e.g., ION904, a subject has, or is at risk for, heart failure, and has a systolic blood pressure less than about 90 mm Hg. In certain embodiments of methods provided herein that include administering to a subject an oligomeric agent, e.g., ION904, the subject is not being treated concurrently with an anti-hypertensive treatment.

[0566] In certain embodiments of methods provided herein that include administering to a subject an oligomeric agent (or salt thereof), e.g., ION904, a subject has, or is at risk for, heart failure, and has an elevated or high potassium level (e.g., blood, plasma or serum potassium level). In certain embodiments, the subject has a serum potassium level greater than about 4.0 mEq/L, greater than about 4.5 mEq/L, greater than about 5.0 mEq/L, or about 5.5 mEq/L or more.

[0567] In certain embodiments of methods provided herein that include administering to a subject an oligomeric agent (or salt thereof), e.g., ION904, a subject has, or is at risk for, heart failure, and has renal dysfunction or renal insufficiency. In certain embodiments, the subject has an estimated glomerular filtration rate (eGFR) between 30 and 90 ml/min/1.73 m², between 30 and 89 ml/min/1.73 m², between 30 and 80 ml/min/1.73 m², between 20 and 89 ml/min/1.73 m², between 20 and 80 ml/min/1.73 m², between 45 and 89 ml/min/1.73 m², between 40 and 89 ml/min/1.73 m², between 40 and 80 ml/min/1.73 m², between 60 and 89 ml/min/1.73 m², between 30 and 60 ml/min/1.73 m², between 30 and 59 ml/min/1.73 m², between 40 and 60 ml/min/1.73 m², between 30 and 44 ml/min/1.73 m², between 35 and 45 ml/min/1.73 m², between 15 and 44 ml/min/1.73 m²,

or between 15 and 29 ml/min/1.73 m². In certain embodiments, the subject has an eGFR less than about 90 ml/min/1.73 m², less than about 89 ml/min/1.73 m², less than about 80 ml/min/1.73 m², less than about 70 ml/min/1.73 m², less than about 60 ml/min/1.73 m², less than about 59 ml/min/1.73 m², less than about 45 ml/min/1.73 m², less than about 44 ml/min/1.73 m², less than about 40 ml/min/1.73 m², less than about 30 ml/min/1.73 m², less than about 29 ml/min/1.73 m², or less than about 15 ml/min/1.73 m².

[0568] In certain embodiments of methods provided herein that include administering to a subject an oligomeric agent (or salt thereof), e.g., ION904, a subject has, or is at risk for, heart failure, and has angioedema or a history of angioedema. In certain embodiments of methods provided herein that include administering to a subject an oligomeric agent, e.g., ION904, a subject has, or is at risk for, heart failure, and has pulmonary disease. In certain embodiments of methods provided herein that include administering to a subject an oligomeric agent, e.g., ION904, a subject has, or is at risk for, heart failure, and has asthma or chronic obstructive pulmonary disease (COPD).

[0569] Methods of reducing the amount of AGT RNA and/or AGT protein in a cell or subject are also provided herein. In certain embodiments, such methods include administering an oligomeric agent or salt thereof (e.g., a unit dose), e.g., ION904, that contains an oligonucleotide (e.g., comprising a nucleobase sequence consisting of 16-30 nucleosides), e.g., a modified oligonucleotide, having a nucleobase sequence complementary to a nucleobase sequence of an equal length target region in an AGT nucleic acid, e.g., a human AGT nucleic acid such as, e.g., SEQ ID NO: 1 or 2, to a cell or subject. In certain embodiments, the oligomeric agent is any one of such oligomeric agents described herein and/or containing any of the oligonucleotides described herein. In certain embodiments, the methods of reducing the amount of AGT RNA and/or AGT protein include administering the oligomeric agent, e.g., ION904, to a subject having or at risk for heart failure, e.g., HFrEF, HFmrEF, HFimpEF or HFpEF. In certain embodiments, the subject is any subject having or at risk for heart failure described herein, including, for example, a subject having or at risk for heart failure and who is, or is at risk of being, intolerant to treatment with a renin-angiotensin-aldosterone system (RAAS) inhibitor. In certain embodiments of the methods, the amount of AGT RNA and/or AGT protein in the cell or subject is decreased after administering the oligomeric agent, e.g., ION904, compared to the baseline amount of AGT RNA and/or AGT protein in the cell or subject prior to any administration of the oligomeric agent. In certain embodiments, the amount or level of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT

protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) decreases by at least 70%, at least 75%, at least 80%, or at least 85% compared to the amount or level of AGT RNA and/or AGT protein compared to the baseline amount of AGT RNA and/or AGT protein in the cell or subject prior to any administration of the oligomeric agent. In certain embodiments, the maximum decrease in the amount or level of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT protein) is less than 95%, or less than 94%, or less than 93%, or less than 92%, or less than 91%, or less than 90% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, the amount or level of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT protein) decreases no more than 85%, or no more than 86%, or no more than 87%, or no more than 88%, or no more than 89%, or no more than 90%, or no more than 91%, or no more than 92%, or no more than 93%, or no more than 94%, or no more than 95%, compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) decreases by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) decreases by at least 70%, at least 75%, at least 80% or at least 85% and less than 94% compared to the baseline amount or level of AGT RNA and/or AGT protein in a cell or subject. In certain embodiments, the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) decreases by at least 70%, at least 75%, at least 80% or at least 85% and less than 93% compared to the baseline amount or level of AGT RNA and/or AGT protein in a cell or subject. In certain embodiments, the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) decreases by at least 70%, at least 75%, at least 80% or at least 85% and less than 92% compared to the baseline amount or level of AGT RNA and/or AGT protein in the cell or

subject. In certain embodiments, the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) decreases by at least 70%, at least 75%, at least 80% or at least 85% and less than 91% compared to the baseline amount or level of AGT RNA and/or AGT protein in a cell or subject. In certain embodiments, the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) decreases by at least 70%, at least 75%, at least 80% or at least 85% and less than 90% compared to the baseline amount or level of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) decreases by at least 70%, at least 75%, at least 80% or at least 85% and less than 89% compared to the baseline amount or level of AGT RNA and/or AGT protein in the cell or subject.

[0570] In certain embodiments methods of reducing the amount of AGT RNA and/or AGT protein in a cell or subject include administering an oligomeric agent or salt thereof (e.g., a unit dose), e.g., ION904, to a cell or subject, wherein the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) decreases by at least 70% but less than 95%, less than 94%, less than 93%, less than 92%, less than 91%, less than 90%, less than 89%, less than 88%, or less than 85% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) decreases by at least 75% but less than 95%, less than 94%, less than 93%, less than 92%, less than 91%, less than 90%, less than 89%, less than 88%, or less than 85% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) decreases by at least 80% but less than 95%, less than 94%, less than 93%, less than 92%, less than 91%, less than 90%, less than 89%, less than 88%, or less than 85% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, the amount of AGT RNA and/or AGT protein in the

cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) decreases by at least 85% but less than 95%, less than 94%, less than 93%, less than 92%, less than 91%, less than 90%, or less than 89% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, the amount of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) decreases by 70%-90%, 70%-89%, 70%-88%, 70%-87%, 70%-86%, 70%-85%, 70%-84%, 70%-83%, 70%-82%, 70%-81%, 70%-80%, 75%-90%, 75%-89%, 75%-88%, 75%-87%, 75%-86%, 75%-85%, 75%-84%, 75%-83%, 75%-82%, 75%-81%, 75%-80%, 76%-90%, 76%-89%, 76%-88%, 76%-87%, 76%-86%, 76%-85%, 76%-84%, 76%-83%, 76%-82%, 76%-81%, 76%-80%, 77%-90%, 77%-89%, 77%-88%, 77%-87%, 77%-86%, 77%-85%, 77%-84%, 77%-83%, 77%-82%, 77%-81%, 77%-80%, 78%-90%, 78%-89%, 78%-88%, 78%-87%, 78%-86%, 78%-85%, 78%-84%, 78%-83%, 78%-82%, 78%-81%, 78%-80%, 79%-90%, 79%-89%, 79%-88%, 79%-87%, 79%-86%, 79%-85%, 79%-84%, 79%-83%, 79%-82%, 79%-81%, 79%-80%, 80%-90%, 80%-89%, 80%-88%, 80%-87%, 80%-86%, 80%-85%, 80%-84%, 80%-83%, 80%-82%, 81%-90%, 81%-89%, 81%-88%, 81%-87%, 81%-86%, 81%-85%, 81%-84%, 81%-83%, 81%-82%, 82%-90%, 82%-89%, 82%-88%, 82%-87%, 82%-86%, 82%-85%, 82%-84%, 82%-83%, 83%-90%, 83%-89%, 83%-88%, 83%-87%, 83%-86%, 83%-85%, 83%-84%, 84%-90%, 84%-89%, 84%-88%, 84%-87%, 84%-86%, 84%-85%, 85%-90%, 85%-89%, 85%-88%, 85%-87%, 85%-86%, 86%-90%, 86%-89%, 86%-88%, 86%-87%, 87%-90%, 87%-89%, 87%-88%, 88%-90%, or 88%-89% compared to the baseline level or amount of AGT RNA and/or AGT protein in the cell or subject. In certain embodiments, the oligomeric agent is administered once every month (or once every four weeks), or once every 28 days, or once every two weeks, or once every week.

[0571] Methods of treating heart failure and/or ameliorating one or more symptoms of heart failure are also provided herein. In certain embodiments of such methods, at least one symptom of fatigue, rapid or irregular heartbeat, palpitation, shortness of breath, chest pain, dizziness, weakness, dyspnea, orthopnea, edema, hepatic congestion, or ascites is ameliorated or prevented. In certain embodiments, treatment delays the onset of, slows the progression of, or prevents heart failure or a symptom thereof. In certain embodiments, such methods include administering an oligomeric agent or salt thereof (e.g., a unit dose), e.g., ION904, that contains an oligonucleotide (e.g., comprising a nucleobase sequence consisting of 16-30 nucleosides), e.g., a modified oligonucleotide, having a

nucleobase sequence complementary to a nucleobase sequence of an equal length target region in an AGT nucleic acid, e.g., a human AGT nucleic acid such as, e.g., SEQ ID NO: 1 or 2, to subject. In certain embodiments, the oligomeric agent is any one of such oligomeric agents described herein and/or containing any of the oligonucleotides described herein. In certain embodiments, the methods of treating heart failure and/or ameliorating one or more symptoms of heart failure include administering the oligomeric agent, e.g., ION904, to a subject having or at risk for heart failure, e.g., HFrEF, HFmrEF, HFimpEF or HFpEF. In certain embodiments, the subject is any subject having or at risk for heart failure described herein, including, for example, a subject having or at risk for heart failure and who is, or is at risk of being, intolerant to treatment with a renin-angiotensin-aldosterone system (RAAS) inhibitor. In certain embodiments of the methods of treating heart failure and/or ameliorating one or more symptoms of heart failure, the amount of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) is reduced, for example, by any of the percentages described herein. In certain embodiments of the methods treating heart failure and/or ameliorating one or more symptoms of heart failure, and of the methods of reducing the amount of AGT RNA and/or AGT protein in a subject, administration of the oligomeric agent, e.g., ION904, treats, and/or ameliorates one or more symptoms of, heart failure in the subject but does not significantly alter (e.g., decrease) systemic blood pressure (e.g., systolic blood or diastolic blood pressure) in the subject having, or at risk for, heart failure, e.g., HFrEF. In certain embodiments, the subject having, or at risk for, heart failure, has hypotension (low blood pressure) or normotension (normal blood pressure). In certain embodiments, the oligomeric agent, e.g., ION904, is administered once every month (or once every four weeks), once every 28 days, or once every two weeks, or once every week. In certain embodiments, a significant alteration in systolic or diastolic blood pressure is a greater than about 10 mm Hg change in blood pressure, or a greater than about 11 mm Hg change in blood pressure, or a greater than about 12 mm Hg change in blood pressure, or a greater than about 13 mm Hg change in blood pressure, or a greater than about 14 mm Hg change in blood pressure, or a greater than about 15 mm Hg change in blood pressure. In certain embodiments, normal systolic blood pressure is within the range of about 90 mm Hg or 100 mm Hg to about 120 mm Hg or 125 mm Hg, and normal diastolic blood pressure is within the range of about 60 mm Hg and about 80 mm Hg. In certain embodiments, low systolic blood pressure is less than about 90 mm Hg and low diastolic blood pressure is less than about 60 mm Hg. In certain

embodiments, elevated systolic blood pressure is about 125 mm Hg to about 129 mm Hg and high systolic blood pressure (i.e., hypertension) is about 130 mm Hg or higher.

[0572] In certain embodiments of the methods treating heart failure and/or ameliorating one or more symptoms of heart failure, and of the methods of reducing the amount of AGT RNA and/or AGT protein in a subject, administration of the oligomeric agent (or salt thereof), e.g., ION904, treats, and/or ameliorates one or more symptoms of, heart failure in the subject but does not significantly alter (e.g., increase) potassium levels (e.g., blood, serum or plasma potassium levels) in the subject having, or at risk for, heart failure, e.g., HFrEF. In certain embodiments, the subject having, or at risk for, heart failure has hyperkalemia, renal dysfunction, or renal insufficiency, acute kidney injury (AKI), or chronic kidney disease (CKD). In certain embodiments, the oligomeric agent, e.g., ION904, is administered once every month (or once every four weeks), once every 28 days, or once every two weeks, or once every week. In certain embodiments, hyperkalemia is a high potassium level (e.g., serum potassium level) of greater than about 5.0 mEq/L or about 5.5 mEq/L, elevated serum potassium level is greater than about 4.0 mEq/L, and normal potassium levels are within the range of about 3.5 mEq/L to about 5.0 mEq/L. In certain embodiments, renal insufficiency is associated with an eGFR of less than about 90 ml/min/1.73 m² or less than about 100 ml/min/1.73 m² (or eGFR between 30 and 90 ml/min/1.73 m², ≤ 40 ml/min/1.73 m², ≤ 35 ml/min/1.73 m², or ≤ 30 ml/min/1.73 m²), stage 2 kidney disease is associated with an eGFR within the range of about 60 ml/min/1.73 m² to about 89 ml/min/1.73 m², stage 3 kidney disease is associated with an eGFR within the range of about 30 ml/min/1.73 m² to about 59 ml/min/1.73 m², stage 4 kidney disease is associated with an eGFR within the range of about 15 ml/min/1.73 m² to about 29 ml/min/1.73 m², and stage 5 kidney disease (kidney failure) is associated with an eGFR of less than about 15 ml/min/1.73 m².

[0573] In certain embodiments of the methods treating heart failure and/or ameliorating one or more symptoms of heart failure, and of the methods of reducing the amount of AGT RNA and/or AGT protein in a subject, administration of the oligomeric agent (or salt thereof), e.g., ION904, treats, and/or ameliorates one or more symptoms of, heart failure in the subject but does not significantly alter bradykinin homeostasis and/or increase bradykinin levels (e.g., blood, serum, or plasma bradykinin levels) in the subject having, or at risk for heart failure, e.g., HFrEF. In certain embodiments, the subject having, or at risk for heart failure has pulmonary disease or angioedema.

In certain embodiments, the oligomeric agent, e.g., ION904, is administered once every month (or once every four weeks), once every 28 days, or once every two weeks, or once every week.

[0574] In certain embodiments of the methods treating heart failure and/or ameliorating one or more symptoms of heart failure, and of the methods of reducing the amount of AGT RNA and/or AGT protein in a subject, administration of the oligomeric agent (or salt thereof), e.g., ION904, improves cardiac function, reduces cardiac dilation, reduces cardiac fibrosis, reverses or attenuates cardiac remodeling, and/or increases LVEF in a subject having, or at risk for, heart failure (such as HFrEF, HFmrEF or HFpEF). In certain embodiments, administration of the oligomeric agent, e.g., ION904, improves left ventricular end diastolic volume (LVEDV), improves left ventricle (LV) strain, improves a 6-minute walk test, and/or improves quality of life as assessed by patient reported outcomes of a subject having, or at risk for, heart failure. In certain embodiments administration of the oligomeric agent, e.g., ION904, improves left ventricular ESVi or LVESV of a subject having, or at risk for, heart failure (such as HFrEF, HFmrEF or HFpEF). In certain embodiments, administration of the oligomeric agent, e.g., ION904, decreases the level of NT-proBNP, BNP, high-sensitive cardiac troponin T (hs-cTnT), and/or cTnT in plasma of a subject having, or at risk for, heart failure (such as HFrEF, HFmrEF or HFpEF) compared to the baseline level in a subject before any administration of the oligomeric agent, e.g., ION904. In certain embodiments, the oligomeric agent, e.g., ION904, is administered once every month (or once every four weeks), once every 28 days, or once every two weeks, or once every week.

[0575] In certain embodiments of the methods that include administering an oligomeric agent or salt thereof (e.g., a unit dose), e.g., ION904, that contains an oligonucleotide (e.g., comprising a nucleobase sequence consisting of 16-30 nucleosides), e.g., a modified oligonucleotide, having a nucleobase sequence complementary to a nucleobase sequence of an equal length target region in an AGT nucleic acid, e.g., a human AGT nucleic acid such as, e.g., SEQ ID NO: 1 or 2, to a cell or subject, a certain quantity, unit dose, or dose of the oligomeric agent is administered to the cell or subject. Included in such methods are embodiments of methods provided herein for treating heart failure and/or ameliorating one or more symptoms of heart failure, and methods of reducing the amount of AGT RNA and/or AGT protein in a cell or subject. In certain embodiments, the quantity of the oligomeric agent, or the quantity of oligomeric agent in the dose or unit dose, is about 15 mg to about 200 mg of ION904. In certain embodiments, a dose of an oligomeric agent, e.g., ION904, administered is a fixed dose. In certain embodiments, a dose of an oligomeric agent, e.g., ION904, is

a loading dose or maintenance dose as described herein. In certain embodiments, a quantity, unit dose, or dose of an oligomeric agent, e.g., ION904, is a specific quantity of the oligomeric agent, e.g., ION904, as described herein. For example, in certain embodiments of the methods that include administering an oligomeric agent (e.g., a unit dose), e.g., ION904, the methods for treating heart failure and/or ameliorating one or more symptoms of heart failure, and the methods of reducing the amount of AGT RNA and/or AGT protein in a cell or subject, the quantity of an oligomeric agent, e.g., ION904, administered is within the range of about 60 mg to about 110 mg, about 75 mg to about 110 mg, about 85 mg to about 110 mg, about 90 mg to about 110 mg, about 95 mg to about 110 mg, about 100 mg to about 110 mg, about 80 mg to about 100 mg, about 85 mg to about 100 mg, or about 90 mg to about 100 mg. In certain embodiments, the quantity of the oligomeric agent, e.g., ION904, in a dose (e.g., a unit dose) is 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, or about 120 mg. In certain embodiments, the quantity of the oligomeric agent, e.g., ION904, in a dose (e.g., a unit dose) is 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 105 mg, 110 mg, or 120 mg. In certain embodiments, the quantity of the oligomeric agent, e.g., ION904, is 80 mg to 120 mg. In certain embodiments, the quantity of the oligomeric agent is administered once every month, once every four weeks, or once every 28 days.

[0576] In certain embodiments of the methods that include administering an oligomeric agent or salt thereof (e.g., a unit dose), e.g., ION904, the methods for treating heart failure and/or ameliorating one or more symptoms of heart failure, and the methods of reducing the amount of AGT RNA and/or AGT protein in a cell or subject, the oligomeric agent, e.g., ION904, is administered to cell or subject one time, at least two times, two or more times, or a plurality of times. In certain embodiments, the oligomeric agent, e.g., ION904, is administered to a subject more than once, e.g., at least two times or two or more times, and the administrations of the oligomeric agent are separated by a period of time in a dosing regimen. In certain embodiments, the doses of oligomeric agent, e.g., ION904, administered at separate times can be the same or different. In certain embodiments, the oligomeric agent is administered repeatedly for a certain period of time (e.g., treatment period or treatment duration). In certain embodiments, the quantity or dose (e.g., a unit dose) is any of the particular doses or amounts described herein. In certain embodiments, the oligomeric agent, e.g., ION904, is administered in a dosing regimen for reducing the level or amount of AGT RNA and/or AGT protein in a subject (e.g., the amount of AGT protein in the

blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein), for example, for reducing the level or amount of AGT RNA and/or AGT protein in a subject by certain percentages described herein. In certain embodiments, the oligomeric agent, e.g., ION904, is administered in a dosing regimen for treating, and/or ameliorating one or more symptoms of heart failure in, a subject having or at risk for heart failure, such as HFrEF, HFpEF, HFimpEF, or HFmrEF. In certain embodiments, the subject has or is at risk for HFrEF. In certain embodiments of the methods that include administering an oligomeric agent (e.g., a unit dose), e.g., ION904, the methods for treating heart failure and/or ameliorating one or more symptoms of heart failure, and the methods of reducing the amount of AGT RNA and/or AGT protein in a cell or subject, the oligomeric agent, e.g., ION904, the oligomeric agent, e.g., ION904, is administered at any of the frequencies, durations of time (e.g., treatment periods) and in any of the quantities, unit doses or doses described herein. For example, in certain embodiments, the oligomeric agent, e.g., ION904, is administered about once every 4 weeks. In certain embodiments, a method comprises administering to a subject 90 mg of oligomeric agent, e.g., ION904, once every 4 weeks. In certain embodiments a method comprises administering to a subject about 100 mg of oligomeric agent, e.g., ION904, about once every 4 weeks. In certain embodiments a method comprises administering to a subject 100 mg of oligomeric agent, e.g., ION904, once every 4 weeks. In certain embodiments a method comprises administering to a subject about 90 mg of oligomeric agent, e.g., ION904, subcutaneously about once every 4 weeks. In certain embodiments a method comprises administering to a subject 90 mg of oligomeric agent, e.g., ION904, subcutaneously once every 4 weeks. In certain embodiments a method comprises administering to a subject about 100 mg of oligomeric agent, e.g., ION904, subcutaneously about once every 4 weeks. In certain embodiments a method comprises administering to a subject 100 mg of oligomeric agent, e.g., ION904, subcutaneously once every 4 weeks. In certain embodiments, methods comprise administering the oligomeric agent, e.g., ION904 (e.g., a unit dose of the oligomeric agent), for as long as required to decrease the amount or level of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein) to a desired level and/or to maintain a desired amount or level of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein). In certain embodiments, methods comprise administering the oligomeric agent, e.g., ION904 (e.g., a unit dose of the oligomeric agent), for as

long as the subject needs treatment for, and/or amelioration of one or more symptoms of, heart failure, such as HFrEF, HFpEF, or HFmrEF.

[0577] In certain embodiments of the methods that include administering an oligomeric agent or salt thereof (e.g., a unit dose), e.g., ION904, the methods for treating heart failure and/or ameliorating one or more symptoms of heart failure, and the methods of reducing the amount of AGT RNA and/or AGT protein in a cell or subject, in which the oligomeric agent, e.g., ION904, is administered to a cell or subject more than once (e.g., two or more times or at least two times) over a certain time period or duration of treatment or treatment time period, the quantity of the oligomeric agent administered at any particular time is changed depending on the level of AGT RNA and/or AGT protein in the cell or subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein). In certain embodiments, the method includes administering a quantity (e.g., dose, unit dose) of the oligomeric agent, e.g., ION904, to a subject, and, after a period of time, and before administering another unit dose or quantity of the oligomeric agent, determining, or measuring, the amount of AGT RNA and/or AGT protein in the subject (e.g., the amount of AGT protein in the blood, serum or plasma of the subject, or the circulating level of AGT RNA and/or AGT protein). If the amount of AGT RNA and/or AGT protein in the subject is less than a predetermined level, then the quantity of the oligomeric agent in the next unit dose administered to the subject is decreased (i.e., the dose of oligomeric agent is decreased) relative to the previous dose and/or the administration of the next unit dose is delayed until the amount of AGT RNA and/or AGT protein in the subject increases. If, instead, the amount of AGT RNA and/or AGT protein in the subject is greater than a predetermined level, then the quantity of the oligomeric agent in the next unit dose administered to the subject is increased (i.e., the dose of oligomeric agent is increased) relative to the previous dose and/or the administration of one or more subsequent unit doses is moved up in time or the frequency of administration of subsequent unit doses is increased at least until the amount of AGT RNA and/or AGT protein in the subject decreases. In certain embodiments of these methods, the predetermined level of AGT RNA and/or AGT protein, represented, for example, as a certain percentage of the amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent (e.g., the baseline level of AGT RNA and/or AGT protein in the subject), is any of the predetermined levels described for such methods herein. In certain embodiments of these methods, the period of time after administering the oligomeric agent, and before administering another unit dose or quantity of

the oligomeric agent, at which the amount of AGT RNA and/or AGT protein is measured is any such time periods described for such methods herein. In certain embodiments of these methods, the subject is any subject having or at risk for heart failure described herein, including, for example, a subject having or at risk for heart failure and who is, or is at risk of being, intolerant to treatment with a renin-angiotensin-aldosterone system (RAAS) inhibitor.

[0578] In certain embodiments of any of the methods (including embodiments of methods for treating heart failure and/or ameliorating one or more symptoms of heart failure, and methods of reducing the amount of AGT RNA and/or AGT protein in a cell or subject) that include administering an oligomeric agent or salt thereof (e.g., a unit dose), e.g., ION904, that contains an oligonucleotide (e.g., comprising a nucleobase sequence consisting of 16-30 nucleosides), e.g., a modified oligonucleotide, having a nucleobase sequence complementary to a nucleobase sequence of an equal length target region in an AGT nucleic acid, e.g., a human AGT nucleic acid such as, e.g., SEQ ID NO: 1 or 2, to a cell or subject, the oligomeric agent is contained within a composition, e.g., a pharmaceutical composition. In certain embodiments, a pharmaceutical composition comprises a pharmaceutically acceptable carrier or excipient. In certain embodiments, the pharmaceutical composition consists of, or consists essentially of, the oligomeric agent (e.g., a unit dose), e.g., ION904, and a pharmaceutically acceptable carrier or excipient. In certain embodiments, the pharmaceutical composition comprises, consists of, or consists essentially of a sterile saline solution (e.g., pharmaceutical grade saline) and the oligomeric agent. In certain embodiments, the pharmaceutical composition comprises, consists of, or consists essentially of sterile water (e.g., pharmaceutical grade water) and the oligomeric agent, ION904. In certain embodiments, the pharmaceutical composition comprises, consists of, or consists essentially of the oligomeric agent, e.g., ION904, in 2mM phosphate buffered isotonic saline, pH 7.4. In certain embodiments of the methods of administering an oligomeric agent (or salt thereof), e.g., ION904, the methods for treating heart failure and/or ameliorating one or more symptoms of heart failure, and the methods of reducing the amount of AGT RNA and/or AGT protein in a cell or subject, the oligomeric agent or salt thereof, ION904, or pharmaceutical composition is administered parenterally. In certain embodiments, the oligomeric agent or salt thereof, ION904, or pharmaceutical composition is administered subcutaneously. In certain embodiments, the oligomeric agent or salt thereof, ION904, or pharmaceutical composition is administered by a syringe. In certain embodiments, the oligomeric

agent or salt thereof, ION904, or pharmaceutical composition is administered by an autoinjector device.

[0579] In certain embodiments of the methods provided herein for administering an oligomeric agent or salt thereof (e.g., a unit dose), e.g., ION904, the methods for treating heart failure and/or ameliorating one or more symptoms of heart failure, and the methods of reducing the amount of AGT RNA and/or AGT protein in a cell or subject, the method comprises administering the oligomeric agent and administering a different active agent. In certain embodiments, the oligomeric agent and the different active agent are administered concurrently. In certain embodiments, the different agent is one that, together with the oligomeric agent that contains a modified oligonucleotide having a nucleobase sequence complementary to a nucleobase sequence of an equal length target region in an AGT nucleic acid, e.g., a human AGT nucleic acid such as, e.g., SEQ ID NO: 1 or 2, produces a combinational effect or a synergistic effect, for example, in reducing the amount of AGT RNA and/or AGT protein in the subject or in treating heart failure and/or ameliorating one or more symptoms of heart failure. In certain embodiments, the method includes administering to the subject the oligomeric agent, e.g., ION904, and administering to the subject another RAAS inhibitor. In certain embodiments, the method includes administering to the subject the oligomeric agent, e.g., ION904, and administering to the subject one or more of an ACEi, ARB, ARNi or MRA. In certain embodiments, the method includes administering to the subject the oligomeric agent, e.g., ION904, and administering to the subject a GDMT for heart failure, e.g., HFrEF. In certain embodiments, the GDMT for heart failure is one from each category of: i) ACEi, ARB, ARNi, ii) MRA, iii) beta blocker and iv) SGLT2. In certain embodiments, the method includes administering the oligomeric agent, e.g., ION904, to the subject and administering a dose of an ACEi, ARB, ARNi and/or an MRA that is less than the Guideline-recommended dose (or dose recognized by the medical community as therapeutic, efficacious, optimal, or fully or maximally efficacious) and/or dosing regimen for treatment of heart failure, e.g., HFrEF (e.g., a dose that is less than 60%, or less than 50%, or less than 40% of the Guideline-recommended dose and/or optimal dose for treatment of HFrEF and/or an administration frequency or duration of treatment that is less than the Guideline-recommended dose or optimal administration frequency or treatment period). In certain embodiments, the method includes administering the oligomeric agent, e.g., ION904, to the subject and administering to the subject a neprilysin inhibitor, such as, for example, sacubitril (e.g., about 40 to about 100 mg) or a modified oligonucleotide (such as, for example, a single-stranded

modified oligonucleotide) having a nucleobase sequence complementary to a sequence in a neprilysin nucleic acid (e.g., a modified antisense oligonucleotide targeting a human neprilysin (MME) RNA). In certain embodiments, the subject is being treated concurrently with a neprilysin inhibitor and is not being treated concurrently with an ACEi or ARB, or with any other RAAS inhibitor. In certain embodiments, the method includes administering the oligomeric agent, e.g., ION904, to the subject and administering a neprilysin inhibitor to the subject wherein the subject is not being treated concurrently with any other GDMT for heart failure. In certain embodiments of concurrent administration, the oligomeric agent, e.g., ION904, and the at least one other active agent are administered simultaneously (i.e., within the same 24-hour period). In certain embodiments, the oligomeric agent, e.g., ION904, and the at least one other active agent may be contained together in a single formulation or composition, or may be separate compositions. In certain embodiments of concurrent administration, the oligomeric agent, e.g., ION904, and the at least one other active agent are administered sequentially (i.e., more than 24 hours apart). In certain embodiments, the method includes administering the oligomeric agent, e.g., ION904, to the subject and administering to the subject an angiotensin receptor blocker-neprilysin inhibitor (ARNi), such as, for example, the ARB valsartan with sacubitril, a neprilysin inhibitor Ni (e.g., about 25 to about 100 mg, e.g., about 24-26 mg, 48-52 mg, 96-104 mg). In certain embodiments, the subject is being treated concurrently with a ARNi and is not being treated concurrently with an ACEi or with any other RAAS inhibitor. In certain embodiments, the method includes administering the oligomeric agent, e.g., ION904, to the subject and administering a ARNi to the subject wherein the subject is not being treated concurrently with any other GDMT for heart failure. In certain embodiments of concurrent administration, the oligomeric agent, e.g., ION904, and the at least one other active agent are administered simultaneously (i.e., within the same 24-hour period). In certain embodiments, the oligomeric agent, e.g., ION904, and the at ARNi active agent may be contained together in a single formulation or composition, or may be separate compositions. In certain embodiments of concurrent administration, the oligomeric agent, e.g., ION904, and the ARNi active agent are administered sequentially (i.e., more than 24 hours apart).

[0580] In certain embodiments, an active agent that may be administered concurrently with an oligomeric agent, e.g., ION904, is an ACE inhibitor (e.g., lisinopril, ramipril, perindopril, enalapril, benazepril, quinapril, captopril, fosinopril, trandolapril, moexipril, enalaprilat, trandolapril), an ARB (e.g., losartan, olmesartan, valsartan, candesartan, irbesartan, telmisartan, azilsartan, eprosartan), a

beta blocker (e.g., bisoprolol, carvedilol, carvedilol CR, metoprolol), a calcium channel blocker, a non-potassium sparing diuretic, an alpha-1 blocker, centrally acting sympatholytic agent, SGLT2 inhibitor (SGLT2i, e.g., empagliflozin, canagliflozin, dapagliflozin, ertugliflozin), a direct acting vasodilator (e.g. hydralazine), or a neprilysin inhibitor (e.g., sacubitril), or combination of any of the agents.

[0581] In certain embodiments, methods described herein, including methods for administering an oligomeric agent or salt thereof (e.g., a unit dose), e.g., ION904, for treating heart failure and/or ameliorating one or more symptoms of heart failure, or for reducing the amount of AGT RNA and/or AGT protein in a cell or subject, are sufficiently effective to treat heart failure, such as HFrEF, HFpEF, HFimpEF, or HFmrEF, in a human subject. In certain embodiments, methods described herein, including methods for administering an oligomeric agent or salt thereof (e.g., a unit dose), e.g., ION904, for treating heart failure and/or ameliorating one or more symptoms of heart failure, or for reducing the amount of AGT RNA and/or AGT protein in a cell or subject, are sufficiently effective to treat HFrEF in a human subject. In certain embodiments, methods described herein, including methods for administering an oligomeric agent or salt thereof (e.g., a unit dose), e.g., ION904, for treating heart failure and/or ameliorating one or more symptoms of heart failure, or for reducing the amount of AGT RNA and/or AGT protein in a cell or subject, are sufficiently effective to ameliorate or prevent one or more symptoms of heart failure, such as HFrEF, HFpEF, HFimpEF, or HFmrEF, in a human subject. In certain embodiments, methods described herein, including methods for administering an oligomeric agent or salt thereof (e.g., a unit dose), e.g., ION904, for treating heart failure and/or ameliorating one or more symptoms of heart failure, or for reducing the amount of AGT RNA and/or AGT protein in a cell or subject, are sufficiently effective to ameliorate or prevent one or more symptoms of HFrEF in a human subject.

[0582] In certain embodiments, a method of treating, and/or ameliorating one or more symptoms of, heart failure, such as HFrEF, HFpEF, HFimpEF, or HFmrEF, comprises administering ION904 (e.g., a unit dose of ION904) once every 4 weeks to a subject having or at risk for heart failure, thereby treating, and/or ameliorating one or more symptoms of, heart failure in the subject. In certain embodiments, a method of treating, and/or ameliorating one or more symptoms of HFrEF comprises administering ION904 (e.g., a unit dose of ION904) once every 4 weeks to a subject having or at risk for HFrEF, thereby treating, and/or ameliorating one or more symptoms of, HFrEF in the subject.

[0583] In certain embodiments, a method of treating, and/or ameliorating one or more symptoms of, heart failure, such as HFrEF, HFpEF, HFimpEF, or HFmrEF, comprises administering to a subject having or at risk for heart failure about 60 mg of ION904 once every 4 weeks. In certain embodiments, a method of treating, and/or ameliorating one or more symptoms of HFrEF comprises administering to a subject having or at risk for HFrEF about 60 mg of ION904 once every 4 weeks. In certain embodiments, a method of treating, and/or ameliorating one or more symptoms of, heart failure, such as HFrEF, HFpEF, HFimpEF, or HFmrEF, comprises administering to a subject having or at risk for heart failure 60 mg of ION904 once every 4 weeks. In certain embodiments, a method of treating, and/or ameliorating one or more symptoms of, HFrEF comprises administering to a subject having or at risk for heart failure 60 mg of ION904 once every 4 weeks.

[0584] In certain embodiments, a method of treating, and/or ameliorating one or more symptoms of, heart failure, such as HFrEF, HFpEF, HFimpEF, or HFmrEF, comprises administering to a subject having or at risk for heart failure about 80 mg of ION904 once every 4 weeks. In certain embodiments, a method of treating, and/or ameliorating one or more symptoms of, HFrEF comprises administering to a subject having or at risk for HFrEF about 80 mg of ION904 once every 4 weeks. In certain embodiments, a method of treating, and/or ameliorating one or more symptoms of, heart failure, such as HFrEF, HFpEF, HFimpEF, or HFmrEF, comprises administering to a subject having or at risk for heart failure 80 mg of ION904 once every 4 weeks. In certain embodiments, a method of treating, and/or ameliorating one or more symptoms of, HFrEF comprises administering to a subject having or at risk for HFrEF 80 mg of ION904 once every 4 weeks.

[0585] In certain embodiments, a method of treating, and/or ameliorating one or more symptoms of, heart failure, such as HFrEF, HFpEF, HFimpEF, or HFmrEF, comprises administering to a subject having or at risk for heart failure about 60 mg of ION904 subcutaneously once every 4 weeks. In certain embodiments, a method of treating, and/or ameliorating one or more symptoms of, HFrEF comprises administering to a subject having or at risk for HFrEF about 60 mg of ION904 subcutaneously once every 4 weeks. In certain embodiments, a method of treating, and/or ameliorating one or more symptoms of, heart failure, such as HFrEF, HFpEF, HFimpEF, or HFmrEF, comprises administering to a subject having or at risk for heart failure 60 mg of ION904 subcutaneously once every 4 weeks. In certain embodiments, a method of treating, and/or

ameliorating one or more symptoms of, HFrEF comprises administering to a subject having or at risk for HFrEF 60 mg of ION904 subcutaneously once every 4 weeks.

[0586] In certain embodiments, a method of treating, and/or ameliorating one or more symptoms of, heart failure, such as HFrEF, HFpEF, HFimpEF, or HFmrEF, comprises administering to a subject having or at risk for heart failure about 80 mg of ION904 subcutaneously once every 4 weeks. In certain embodiments, a method of treating, and/or ameliorating one or more symptoms of, HFrEF comprises administering to a subject having or at risk for HFrEF about 80 mg of ION904 subcutaneously once every 4 weeks. In certain embodiments, a method of treating, and/or ameliorating one or more symptoms of, heart failure, such as HFrEF, HFpEF, HFimpEF, or HFmrEF, comprises administering to a subject having or at risk for heart failure 80 mg of ION904 subcutaneously once every 4 weeks. In certain embodiments, a method of treating, and/or ameliorating one or more symptoms of, HFrEF comprises administering to a subject having or at risk for HFrEF 80 mg of ION904 subcutaneously once every 4 weeks.

[0587] In certain embodiments, a method of treating, and/or ameliorating one or more symptoms of, heart failure, such as HFrEF, HFpEF, HFimpEF, or HFmrEF, comprises administering to a subject having or at risk for heart failure about 90 mg of ION904 once every 4 weeks. In certain embodiments, a method of treating, and/or ameliorating one or more symptoms of HFrEF comprises administering to a subject having or at risk for HFrEF about 90 mg of ION904 once every 4 weeks. In certain embodiments, a method of treating, and/or ameliorating one or more symptoms of, heart failure, such as HFrEF, HFpEF, HFimpEF, or HFmrEF, comprises administering to a subject having or at risk for heart failure 90 mg of ION904 once every 4 weeks. In certain embodiments, a method of treating, and/or ameliorating one or more symptoms of, HFrEF comprises administering to a subject having or at risk for heart failure 90 mg of ION904 once every 4 weeks.

[0588] In certain embodiments, a method of treating, and/or ameliorating one or more symptoms of, heart failure, such as HFrEF, HFpEF, HFimpEF, or HFmrEF, comprises administering to a subject having or at risk for heart failure about 100 mg of ION904 once every 4 weeks. In certain embodiments, a method of treating, and/or ameliorating one or more symptoms of, HFrEF comprises administering to a subject having or at risk for HFrEF about 100 mg of ION904 once every 4 weeks. In certain embodiments, a method of treating, and/or ameliorating one or more symptoms of, heart failure, such as HFrEF, HFpEF, HFimpEF, or HFmrEF, comprises administering to a subject having or at risk for heart failure 100 mg of ION904 once every 4 weeks.

In certain embodiments, a method of treating, and/or ameliorating one or more symptoms of, HFrEF comprises administering to a subject having or at risk for HFrEF 100 mg of ION904 once every 4 weeks.

[0589] In certain embodiments, a method of treating, and/or ameliorating one or more symptoms of, heart failure, such as HFrEF, HFpEF, HFimpEF, or HFmrEF, comprises administering to a subject having or at risk for heart failure about 90 mg of ION904 subcutaneously once every 4 weeks. In certain embodiments, a method of treating, and/or ameliorating one or more symptoms of, HFrEF comprises administering to a subject having or at risk for HFrEF about 90 mg of ION904 subcutaneously once every 4 weeks. In certain embodiments, a method of treating, and/or ameliorating one or more symptoms of, heart failure, such as HFrEF, HFpEF, HFimpEF, or HFmrEF, comprises administering to a subject having or at risk for heart failure 90 mg of ION904 subcutaneously once every 4 weeks. In certain embodiments, a method of treating, and/or ameliorating one or more symptoms of, HFrEF comprises administering to a subject having or at risk for HFrEF 90 mg of ION904 subcutaneously once every 4 weeks.

[0590] In certain embodiments, a method of treating, and/or ameliorating one or more symptoms of, heart failure, such as HFrEF, HFpEF, HFimpEF, or HFmrEF, comprises administering to a subject having or at risk for heart failure about 100 mg of ION904 subcutaneously once every 4 weeks. In certain embodiments, a method of treating, and/or ameliorating one or more symptoms of, HFrEF comprises administering to a subject having or at risk for HFrEF about 100 mg of ION904 subcutaneously once every 4 weeks. In certain embodiments, a method of treating, and/or ameliorating one or more symptoms of, heart failure, such as HFrEF, HFpEF, HFimpEF, or HFmrEF, comprises administering to a subject having or at risk for heart failure 100 mg of ION904 subcutaneously once every 4 weeks. In certain embodiments, a method of treating, and/or ameliorating one or more symptoms of, HFrEF comprises administering to a subject having or at risk for HFrEF 100 mg of ION904 subcutaneously once every 4 weeks.

[0591] Nonlimiting Disclosure and Incorporation by Reference

[0592] All documents, or portions of documents, cited in this application, including, but not limited to, literature publications, patent publications, 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.

[0593] While certain compounds, compositions, and methods have been described herein with [0594] specificity in accordance with certain embodiments, the following examples serve only to illustrate the

[0595] compounds described herein and are not intended to limit the same. Each of the references, GenBank

[0596] accession numbers, ENSEMBL identifiers, and the like recited in the present application is incorporated herein by reference in its entirety.

[0597] The sequence listing accompanying this filing identifies each nucleic acid sequence as either “RNA” or “DNA” as required; however, one of skill in the art will readily appreciate that designation of “RNA” or “DNA” to describe modified oligonucleotides is, in certain instances, arbitrary. For example, an oligonucleotide comprising a nucleoside comprising a 2'-OH sugar moiety and a thymine base could be described as a DNA having a modified sugar (i.e., 2'-OH in place of one 2'-H of DNA) or as an RNA having a modified base (i.e., thymine (5-methyl uracil) in place of an uracil of RNA); and certain nucleic acid compounds described herein comprise one or more nucleosides comprising modified sugar moieties having 2'-substituent(s) that are neither OH nor H. One of skill in the art will readily appreciate that labeling such nucleic acid compounds “RNA” or “DNA” does not alter or limit the description of such nucleic acid compounds.

[0598] Herein, the description of compounds as having “the nucleobase sequence of” a SEQ ID NO. describes only the nucleobase sequence. Accordingly, absent additional description, such description of compounds by reference to a nucleobase sequence of a SEQ ID NO. does not limit sugar or internucleoside linkage modifications or presence or absence of additional substituents such as a conjugate group. Further, absent additional description, the nucleobases of a compound “having the nucleobase sequence of” a SEQ ID NO. include such compounds having modified forms of the identified nucleobases as described herein.

[0599] Herein, the description of compounds by chemical notation (subscripts and/or superscripts to indicate chemical modifications) without reference to a specific Compound No. include only each noted modification, but may include additional substituents, such as a conjugate group, unless otherwise indicated. For example, the chemical notation of “A_{es}T_{ko}^mC_{ez}G_{ds}C_d” indicates a compound wherein the first nucleoside, which comprises a 2'-MOE sugar moiety (indicated by the “e” subscript) and an unmodified adenine nucleobase, is linked to the second nucleoside via a phosphorothioate linkage (indicated by the “s” subscript); the second nucleoside, which comprises a

cEt sugar moiety (indicated by the “k” subscript) and an unmodified thymine nucleobase, is linked to the third nucleoside via a phosphodiester linkage (indicated by the “o” subscript); the third nucleoside, which comprises a 2’-MOE sugar moiety and a 5-methyl modified cytosine nucleobase (indicated by the “m” superscript), is linked to the fourth nucleoside via a mesyl phosphoramidate linkage (indicated by the “z” subscript); the fourth nucleoside, which comprises a 2’-β-D-deoxyribosyl sugar moiety (indicated by the “d” subscript) and an unmodified guanine nucleobase, is linked to the fifth nucleoside with a phosphorothioate linkage; and the fifth nucleoside comprises a 2’-β-D-deoxyribosyl sugar moiety and an unmodified cytosine nucleobase; and the compound may include additional substituents, such as a conjugate group.

[0600] Herein, where a specific compound (e.g., with reference to a Compound No.) is described by chemical notation, each nucleobase, sugar, and internucleoside linkage of such specific compound is modified only as indicated. Accordingly, in the context of a description of a specific compound having a particular Compound No., “A_{es}T_{ko}^mC_{ez}G_{ds}C_d” indicates a compound wherein the first nucleoside, which comprises a 2’-MOE sugar moiety (indicated by the “e” subscript) and an unmodified adenine nucleobase, is linked to the second nucleoside via a phosphorothioate linkage (indicated by the “s” subscript); the second nucleoside, which comprises a cEt sugar moiety (indicated by the “k” subscript) and an unmodified thymine nucleobase, is linked to the third nucleoside via a phosphodiester linkage (indicated by the “o” subscript); the third nucleoside, which comprises a 2’-MOE sugar moiety and a 5-methyl modified cytosine nucleobase (indicated by the “m” superscript), is linked to the fourth nucleoside via a mesyl phosphoramidate linkage (indicated by the “z” subscript); the fourth nucleoside, which comprises a 2’-β-D-deoxyribosyl sugar moiety (indicated by the “d” subscript) and an unmodified guanine nucleobase, is linked to the fifth nucleoside with a phosphorothioate linkage; and the fifth nucleoside comprises a 2’-β-D-deoxyribosyl sugar moiety and an unmodified cytosine nucleobase; and the compound does not include additional substituents.

[0601] Herein, sugar, internucleoside linkage, and nucleobase modifications may be indicated within a nucleotide or nucleobase sequence (e.g., by superscript or subscript, as shown above) or may be indicated in text accompanying a sequence (e.g., in separate text that appears within or above or below a table of compounds).

[0602] Where a specific compound is described herein by way of a drawn chemical structure, each nucleobase, sugar, and internucleoside linkage of such a specific compound includes only the

modifications indicated in the drawn chemical structure. One of skill will appreciate, however, that drawn compounds may exist in equilibrium between tautomeric forms and/or as salts in equilibrium with protonated or ionic forms. Drawn structures are intended to capture all such forms of such compounds.

[0603] While effort has been made to accurately describe compounds in the accompanying sequence listing, should there be any discrepancies between a description in this specification and in the accompanying sequence listing, the description in the specification and not in the sequence listing is the accurate description.

[0604] The compounds described herein include variations in which one or more atoms are replaced with a non-radioactive isotope or radioactive isotope of the indicated element. For example, compounds herein that comprise hydrogen atoms encompass all possible deuterium substitutions for each of the ^1H hydrogen atoms. Isotopic substitutions encompassed by the compounds herein include but are not limited to: ^2H or ^3H in place of ^1H , ^{13}C or ^{14}C in place of ^{12}C , ^{15}N in place of ^{14}N , ^{17}O or ^{18}O in place of ^{16}O , and ^{33}S , ^{34}S , ^{35}S , or ^{36}S in place of ^{32}S . In certain embodiments, non-radioactive isotopic substitutions may impart new properties on the compound that are beneficial for use as a therapeutic or research tool. In certain embodiments, radioactive isotopic substitutions may make the compound suitable for research or diagnostic purposes such as imaging.

[0605] VI. EXAMPLES

[0606] 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.

[0607] Example 1: Effects of ISIS 757456

[0608] Subjects with Uncontrolled Hypertension

[0609] A double-blind, randomized, placebo-controlled phase 2B trial of compound ISIS 757456 (ClinicalTrials.gov Identifier NCT04714320) was conducted with subjects having uncontrolled hypertension (e.g., a systolic blood pressure (SBP) > 130 mm Hg and ≤ 170 mm Hg on hypertensive medication), on three (3) or more antihypertensive medications. See also WO2022/232650. Subjects were on a stable, maximally tolerated regimen (per Investigator judgement) for at least 1 month prior to screening and were required to maintain such regimen throughout the study. Combinations of antihypertensive medications were selected from: a) angiotensin-converting enzyme inhibitor (ACEi) or Ang II receptor blocker (ARB), b) beta blocker, c) calcium channel

blocker, d) diuretic, e) alpha-1 blocker, f) centrally acting sympatholytic agent, and/or g) direct acting vasodilators (e.g. hydralazine). Participants (randomized 2:1) received once-weekly subcutaneous (SC) treatment with either compound ISIS 757456 (80 mg or 120 mg) or matching placebo. Length of participation in the study was 31 weeks, comprising a 6-week screening period, 12-week treatment period, and a 13-week post-treatment period.

[0610] Primary outcome measure was change in seated automated office systolic blood pressure (SBP) from baseline to study day 85; and secondary outcome measures were changes from baseline in plasma AGT protein for each scheduled post-baseline visit, changes from baseline to day 85 in 24-hour mean SBP measured by ambulatory blood pressure monitoring (ABPM), changes from baseline to day 85 in seated automated office diastolic blood pressure (DBP), and in 24-hour mean DBP measured by ABPM. Similar and significant mean percent plasma AGT protein reductions were observed in subjects receiving 80 mg and 120 mg at study day 85 as compared to placebo. Maximum plasma AGT protein reduction of ~60% was achieved by day 29 after 5 doses of 120 mg of compound ISIS 757456, and a similar maximum reduction of plasma AGT protein was achieved by day 43 after 7 doses of 80 mg of compound ISIS 757456; however, reductions in plasma AGT protein did not result in statistically significant changes in blood pressure, whether SBP, DBP (seated or ambulatory).

[0611] Subjects with Chronic Heart Failure with Reduced Ejection Fraction

[0612] A double-blind, randomized, placebo-controlled phase 2 study (ClinicalTrials.gov Identifier NCT04836182) was conducted to evaluate safety and tolerability and an effect of weekly subcutaneous (SC) injection of compound ISIS 757456 (40 mg, 80 mg, or 120 mg) on plasma AGT protein concentration from baseline to Study Day 85 (Week 13), one week after administration of the final dose of ISIS 757456, in chronic heart failure participants with reduced ejection fraction (HFrEF). See also WO2022/232650. Participants were receiving background standard of care for HFrEF wherein therapy was individually optimized and stable for ≥ 4 weeks before randomization. Each participant was receiving an ACEi, ARB or sacubitril/valsartan. Some participants were also receiving a beta-blocker and/or an MRA. The majority of subjects (52%) enrolled in the study were receiving $< 50\%$ of the guideline-directed medical therapy (GDMT; Heidenreich et al (2022) *Circulation* 145(18):e895-e1032, 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines) dose of standard of care RAAS inhibitor therapy (i.e.,

ACEi, ARB or sacubitril/valsartan) for HFrEF. Inclusion criteria also included an NT-proBNP level of ≥ 600 pg/ml and <8500 pg/ml, left ventricular ejection fraction (LVEF) ≤ 40 and a New York Heart Association (NYHA) functional classification (a system used to characterize symptoms of patients with HF) of class I, II or III (The Criteria Committee of the New York Heart Association (1994) Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels, A Little Brown handbook, 9th edition, no. 57, Dolgin, M., ed.). Primary outcome measure was percent change in plasma AGT protein from baseline to day 85; and secondary outcome measures and exploratory assessments were change (and percent change) from baseline in plasma AGT protein to each scheduled post-baseline visit, absolute level of NT-proBNP, change (and percent change) in NT-proBNP from baseline to each scheduled post-baseline visit, and Kansas City Cardiomyopathy Questionnaire (KCCQ; Spertus et al. (2020) J Am Coll Cardiol 76(20):2379-2390 and DDT COA #000084:

[0613] Kansas City Cardiomyopathy Questionnaire (KCCQ). April 16, 2020 available at: <https://www.fda.gov/drugs/ddt-coa-000084-kansascity-cardiomyopathy-questionnaire-kccq>.

[0614] Dose-dependent reduction in plasma AGT protein compared to baseline was observed in all treated subjects at day 85 (40 mg cohort: 45%, 80 mg cohort: 49%, and 120 mg cohort: 61% reduction in mean plasma AGT protein compared to baseline level). A maximum reduction of 63% in plasma AGT protein was achieved by day 57 after 8 doses of 120 mg of compound ISIS 757456; and a maximum reduction of 49% in plasma AGT protein was achieved by day 85 after 12 doses of 80 mg of compound ISIS 757456 (Table 4, Table 5; values based on analysis of per protocol population n=58). There was no significant change in NT-proBNP levels in any of three treatment groups as compared to placebo group at day 85 (Table 6), and there was also no blood pressure effect, although the number of subjects in the treatment groups was less than the number required in order to identify a statistically significant change in NT-proBNP and blood pressure. There was no hypotension signal observed in mean SBP over time. Furthermore, no hepatic, renal or potassium safety signals were observed.

[0615] Table 4: AGT protein levels in plasma of subjects with HFrEF over time.

	Subject Group – Plasma Angiotensinogen (nmol/L)				
Time Point	Placebo	ISIS 757456 (40 mg)	ISIS 757456 (80 mg)	ISIS 757456 (120 mg)	ISIS 757456 Total
Baseline	(n=17)	(n=9)	(n=19)	(n=13)	(n=41)
Mean	909.8	799.6	772.7	704.2	756.9
Median	(357.2, 86.6) ^a	(294.3, 98.1) ^a	(187.7, 43.1) ^a	(347.3, 96.3) ^a	(266.1, 41.6) ^a
	899.0	782.8	762.1	561.3	723.8
	(688.4, 1083.8) ^b	(651.8, 1068.9) ^b	(662.3, 895.3) ^b	(533.0, 735.1) ^b	(587.8, 893.9) ^b
min/max	379.3/1728.7	266.4/1162.6	350.5/1066.6	187.8/1463.7	187.8/1463.7
Day 15	(n=17)	(n=9)	(n=19)	(n=13)	(n=41)
Mean	874.8	653.7	558.5	448.8	544.6
Median	(293.2, 71.1) ^a	(239.3, 79.8) ^a	(185.1, 42.) ^a	(212.7, 59.0) ^a	(214.9, 33.6) ^a
	910.3	676.5	577.2	407.3	537.8
	(699.2, 1077.3) ^b	(631.7, 785.8) ^b	(443.3, 622.5) ^b	(315.7, 537.8) ^b	(405.6, 667.5) ^b
min/max	376.0/1398.6	195.4/990.8	326.0/1174.5	98.8 - 923.1	7.35/9.08
Day 29	(n=16)	(n=9)	(n=19)	(n=13)	(n=41)
Mean	790.7	516.5	446.7	291.5	412.8
Median	(255.3, 63.8) ^a	(216.9, 72.3) ^a	(197.7, 45.4) ^a	(123.3, 34.2) ^a	(198.3, 31.0) ^a
	828.3	523.9	480.9	270.4	367.9
	(666.0, 936.2) ^b	(482.1, 630.1) ^b	(307.0, 549.7) ^b	(258.2, 318.4) ^b	(266.5, 535.1) ^b
min/max	313.4/1149.6	186.0/873.9	119.2/944.1	70.6/625.1	70.6/944.1
Day 43	(n=17)	(n=9)	(n=18)	(n=13)	(n=40)
Mean	842.9	490.9	438.2	264.5	393.6
Median	(305.2, 74.0) ^a	(187.0, 62.3) ^a	(193.9, 45.7) ^a	(100.1, 27.8) ^a	(187.9, 29.7) ^a
	783.2	471.8	480.7	252.2	382.6
	(730.9, 1081.6) ^b	(446.7, 633.3) ^b	(270.3, 540.8) ^b	(224.5, 294.8) ^b	(237.1, 503.2) ^b
min/max	333.1/1404.2	213.8/770.6	123.5/860.5	81.8/511.1	81.8/860.5
Day 57	(n=15)	(n=9)	(n=17)	(n=13)	(n=39)
Mean	764.4	426.3	402.7	245.8	355.8
Median	(223.4, 57.7) ^a	(169.9, 56.6) ^a	(147.9, 35.9) ^a	(87.5, 24.3) ^a	(154.9, 24.8) ^a
	781.0	401.9	421.4	237.1	345.0
	(631.2, 892.7) ^b	(351.1, 513.8) ^b	(299.3, 533.9) ^b	(201.1, 298.0) ^b	(217.4, 454.6) ^b
min/max	349.8/1185.0	197.4/708.5	115.1/617.0	60.9/408.3	60.9/708.5
Day 71	(n=17)	(n=9)	(n=19)	(n=13)	(n=41)
Mean	793.3	392.6	390.7	292.3	359.9
Median	(283.5, 68.8) ^a	(152.7, 50.9) ^a	(162.9, 37.4) ^a	(148.8, 41.3) ^a	(159.5, 24.9) ^a
	732.3	402.0	426.9	262.6	359.7
	(612.5, 944.8) ^b	(327.4, 436.1) ^b	(224.0, 504.5) ^b	(236.5, 359.7) ^b	(236.5, 459.1) ^b
min/max	391.6/1431.1	130.5/603.4	153.7/644.7	59.8/668.3	59.8/668.3

	Subject Group – Plasma Angiotensinogen (nmol/L)				
Time Point	Placebo	ISIS 757456 (40 mg)	ISIS 757456 (80 mg)	ISIS 757456 (120 mg)	ISIS 757456 Total
Day 85	(n=17)	(n=9)	(n=19)	(n=13)	(n=41)
Mean	807.3	413.7	380.2	260.6	349.6
Median	(274.1, 66.5) ^a 796.1	(167.6, 55.9) ^a 378.9	(159.5, 36.6) ^a 436.1	(91.2, 25.3) ^a 257.4	(153.3, 23.9) ^a 370.8
min/max	(682.2, 960.0) ^b 381.1/1381.7	(370.8, 399.6) ^b 171.8/729.7	(186.6, 525.1) ^b 86.0/572.7	(229.7, 279.5) ^b 56.4/438.9	(229.9, 450.2) ^b 56.4/729.7
Day 92	(n=17)	(n=9)	(n=19)	(n=12)	(n=40)
Mean	752.0	456.9	422.6	298.4	393.1
Median	(269.5, 65.4) ^a 727.0	(163.2, 54.4) ^a 477.0	(181.7, 41.7) ^a 402.1	(109.7, 31.7) ^a 288.4	(168.0, 26.6) ^a 350.3
min/max	(558.3, 823.8) ^b 375.6/1304.5	(446.2, 575.8) ^b 167.6/642.4	(276.3, 570.1) ^b 106.2/733.4	(250.7, 343.7) ^b 77.6/546.1	(268.8, 541.7) ^b 77.6/733.4
Day 99	(n=17)	(n=9)	(n=19)	(n=13)	(n=41)
Mean	786.4	496.3	452.5	390.3	442.4
Median	(239.3, 58.0) ^a 757.3	(158.5, 52.8) ^a 534.9	(172.5, 39.6) ^a 441.8	(131.2, 36.4) ^a 397.9	(158.6, 24.8) ^a 428.7
min/max	(639.5, 876.6) ^b 455.2/1353.1	(428.7, 577.9) ^b 206.9/745.5	(306.9, 618.9) ^b 186.6/716.9	(315.3, 464.7) ^b 105.3/660.4	(315.3, 548.1) ^b 105.3/745.5
Day 120	(n=16)	(n=9)	(n=19)	(n=13)	(n=41)
Mean	765.3	695.6	568.0	509.2	577.4
Median	(242.3, 60.6) ^a 763.3	(271.4, 90.5) ^a 757.0	(164.1, 37.7) ^a 570.5	(204.6, 56.7) ^a 476.0	(210.0, 32.8) ^a 571.5
min/max	(620.2, 847.2) ^b 269.7/1303.0	(578.3, 916.3) ^b 185.7/968.2	(470.1, 649.3) ^b 275.0/915.2	(413.7, 577.0) ^b 78.7/908.2	(431.3, 693.4) ^b 78.7/968.2
Day 148	(n=16)	(n=9)	(n=19)	(n=13)	(n=41)
Mean	816.9	715.4	729.5	539.0	666.0
Median	(326.7, 81.7) ^a 797.5	(263.5, 87.8) ^a 712.3	(282.4, 64.8) ^a 688.3	(171.9, 47.7) ^a 560.1	(257.6, 40.2) ^a 663.9
min/max	(580.2, 1044.5) ^b 276.9/1526.1	(644.1, 899.3) ^b 130.4/1025.1	(546.9, 869.5) ^b 285.4/1426.0	(473.1, 641.5) ^b 141.5/826.9	(546.9, 770.8) ^b 130.4/1426.0

^a(SD, SEM), ^b(P25, P75)

[0616] Table 5: Percent change in plasma AGT protein levels of subjects with HFrEF over time.

Subject Group – Percent Change in Plasma Angiotensinogen from Baseline					
Time Point	Placebo	ISIS 757456 (40 mg)	ISIS 757456 (80 mg)	ISIS 757456 (120 mg)	ISIS 757456 Total
Day 15	(n=17)	(n=9)	(n=19)	(n=13)	(n=41)
Mean	1.8 (34.7, 8.4) ^a	-17.4 (17.5, 5.8) ^a	-25.6 (19.8, 4.5) ^a	-33.5 (21.9, 6.1) ^a	-26.3 (20.4, 3.2) ^a
Median	-10.1 (-15.1, 2.2) ^b	-15.5 (-27.5, -12.7) ^b	-23.6 (-36.1, -10.9) ^b	-44.2 (-47.4, -23.6) ^b	-26.7 (-42.9, -12.7) ^b
min/max	-29.8/103.2	-42.1/15.1	-69.4/16.6	-63.1/4.7	-69.4/16.6
P-value ^c		0.103	0.003	0.004	
Day 29	(n=16)	(n=9)	(n=19)	(n=13)	(n=41)
Mean	-5.8 (34.6, 8.7) ^a	-32.9 (24.6, 8.2) ^a	-40.9 (22.5, 5.2) ^a	-56.4 (9.6, 2.7) ^a	-44.0 (21.4, 3.3) ^a
Median	-11.3 (-25.1, 4.1) ^b	-30.2 (-51.0, -18.0) ^b	-41.0 (-58.9, -21.8) ^b	-54.7 (-58.9, -50.0) ^b	-47.9 (-57.5, -27.9) ^b
min/max	-54.2/94.3	-68.4/10.7	-88.8/-6.3	-82.4/-45.5	-88.8/10.7
P-value ^c		0.012	0.001	<0.001	
Day 43	(n=17)	(n=9)	(n=18)	(n=13)	(n=40)
Mean	-2.3 (32.6, 7.9) ^a	-33.5 (27.6, 9.2) ^a	-40.9 (24.0, 5.7) ^a	-60.2 (8.6, 2.4) ^a	-45.5 (23.3, 3.7) ^a
Median	-6.6 (-22.3, 7.9) ^b	-34.8 (-58.2, -13.6) ^b	-39.6 (-58.2, -30.7) ^b	-61.0 (-65.5, -56.4) ^b	-51.6 (-61.2, -32.3) ^b
min/max	-44.4/94.2	-63.8/7.7	-85.6/12.9	-75.8/-42.6	-85.6/12.9
P-value ^c		0.035	<0.001	<0.001	
Day 57	(n=15)	(n=9)	(n=17)	(n=13)	(n=39)
Mean	-13.7 (21.2, 5.5) ^a	-41.4 (25.7, 8.6) ^a	-44.1 (20.8, 5.1) ^a	-63.0 (9.1, 2.5) ^a	-49.8 (20.9, 3.4) ^a
Median	-16.5 (-31.5, -6.0) ^b	-47.4 (-62.4, -18.4) ^b	-38.7 (-56.0, -29.4) ^b	-62.7 (-67.7, -58.3) ^b	-56.0 (-67.7, -32.6) ^b
min/max	-41.8/30.1	-69.8/-10.3	-77.6/-13.2	-80.9/-44.0	-80.9/-10.3
P-value ^c		<0.001	<0.001	<0.001	
Day 71	(n=17)	(n=9)	(n=19)	(n=13)	(n=41)
Mean	-8.3 (23.8, 5.8) ^a	-48.2 (19.0, 6.3) ^a	-47.2 (22.9, 5.3) ^a	-58.3 (9.5, 2.6) ^a	-50.9 (19.0, 3.0) ^a
Median	-8.4 (-26.5, 5.1) ^b	-51.0 (-63.8, -26.5) ^b	-43.5 (-69.1, -29.0) ^b	-56.1 (-68.4, -50.1) ^b	-51.0 (-68.2, -41.6) ^b
min/max	-46.8/53.1	-71.8/-22.9	-84.4/-10.7	-70.4/-45.3	-84.4/-10.7
P-value ^c		<0.001	<0.001	<0.001	

Subject Group – Percent Change in Plasma Angiotensinogen from Baseline					
Time Point	Placebo	ISIS 757456 (40 mg)	ISIS 757456 (80 mg)	ISIS 757456 (120 mg)	ISIS 757456 Total
Day 85	(n=17)	(n=9)	(n=19)	(n=13)	(n=41)
Mean	-4.2 (36.7, 8.9) ^a	-44.6 (21.3, 7.1) ^a	-48.7 (21.0, 4.8) ^a	-60.9 (9.7, 2.7) ^a	-51.7 (19.0, 3.0) ^a
Median	-14.9 (-27.9, 6.8) ^b	-47.6 (-62.6, -35.5) ^b	-46.6 (-56.0, -33.2) ^b	-63.0 (-69.5, -54.9) ^b	-53.8 (-66.9, -41.2) ^b
min/max	-55.0/105.8	-67.4/-6.8	-91.9/-16.0	-74.6/-43.5	-91.9/-6.8
P-value ^c		0.002	<0.001	<0.001	
Day 92	(n=17)	(n=9)	(n=19)	(n=12)	(n=40)
Mean	-10.8 (31.5, 7.6) ^a	-39.2 (22.4, 7.5) ^a	-43.9 (21.3, 4.9) ^a	-55.6 (11.9, 3.4) ^a	-46.4 (19.8, 3.1) ^a
Median	-14.3 (-31.6, 2.2) ^b	-37.1 (-58.3, -20.5) ^b	-41.5 (-56.6, -27.2) ^b	-58.7 (-61.4, -50.3) ^b	-48.9 (-59.3, -31.1) ^b
min/max	-55.3/70.5	-64.3/-2.0	-90.0/-10.9	-74.5/-28.1	-90.0/-2.0
P-value ^c		<0.001	<0.001	<0.001	
Day 99	(n=17)	(n=9)	(n=19)	(n=13)	(n=41)
Mean	-5.3 (33.0, 8.0) ^a	-34.6 (17.5, 5.8) ^a	-40.1 (19.7, 4.5) ^a	-41.0 (12.5, 3.5) ^a	-39.1 (17.0, 2.7) ^a
Median	-3.9 (-22.9, 5.6) ^b	-40.8 (-48.7, -22.0) ^b	-36.5 (-54.0, -28.6) ^b	-42.9 (-46.5, -38.1) ^b	-40.1 (-48.7, -28.6) ^b
min/max	-53.8/87.5	-54.0/-4.8	-82.5/-0.9	-68.0/-19.7	-82.5/-0.9
P-value ^c		0.019	<0.001	0.001	
Day 120	(n=16)	(n=9)	(n=19)	(n=13)	(n=41)
Mean	-8.8 (32.2, 8.1) ^a	-13.2 (19.1, 6.4) ^a	-23.9 (23.7, 5.4) ^a	-25.8 (19.3, 5.4) ^a	-22.2 (21.5, 3.4) ^a
Median	-11.2 (-29.1, 1.9) ^b	-14.2 (-30.3, -1.6) ^b	-26.3 (-44.7, -8.7) ^b	-31.0 (-35.2, -20.1) ^b	-26.3 (-36.0, -9.4) ^b
min/max	-52.1/88.6	-37.5/17.1	-52.9/32.0	-58.1/17.9	-58.1/32.0
P-value ^c		0.429	0.020	0.012	
Day 148	(n=16)	(n=9)	(n=19)	(n=13)	(n=41)
Mean	-8.4 (30.6, 7.7) ^a	-10.8 (23.4, 7.8) ^a	-5.7 (28.8, 6.6) ^a	-16.6 (24.8, 6.9) ^a	-10.3 (26.3, 4.1) ^a
Median	-4.5 (-30.6, 16.1) ^b	-6.9 (-15.9, 1.0) ^b	-13.9 (-23.1, 0.7) ^b	-15.7 (-32.6, 1.9) ^b	-11.8 (-24.7, 1.0) ^b
min/max	-57.2/44.7	-51.1/22.0	-42.6/68.5	-56.7/29.0	-56.7/68.5
P-value ^c		0.590	0.833	0.166	

^a(SD, SEM), ^b(P25, P75), ^cP-value of ANCOVA with treatment, screening NT-proBNP stratification factor and baseline lab result. If data departs substantially from normality, Van Elteren test was used.

[0617] Table 6: Change in NT-proBNP levels (measured in pg/ml) in plasma of HFrEF subjects.

Subject Group - Percent Change in NT-proBNP Level from Baseline to Day 85					
	Placebo (n=17)	40 mg 757456 (n=9)	80 mg 757456 (n=19)	120 mg 757456 (n=13)	TOTAL 757456 (n=41)
Mean Percent Change (SD, SEM)	19.0 (78.9, 19.1)	29.4 (89.3, 29.8)	15.3 (86.9, 19.9)	9.5 (45.1, 12.5)	16.6 (75.2, 11.7)
Median Percent Change (P25, P75)	-8.9 (-21.5, 19.0)	-7.2 (-28.8, 55.7)	-3.7 (-23.7, 23.0)	-3.0 (-22.9, 23.8)	-3.7 (-23.7, 23.8)

[0618] Example 2: Effect of ION904 in Healthy Volunteers.

[0619] Study Design

[0620] A double blind, randomized, placebo-controlled phase 1 study of ION904 (ClinicalTrials.gov Identifier NCT04731623) was conducted with healthy volunteers assessing safety and tolerability of ION904 in 5 single-ascending dose cohorts (10 mg, 30 mg, 60 mg, 90 mg, and 120 mg). Following a screening period, eligible healthy participants were randomized to treatment (30 subjects treated with ION904 and 10 with placebo) and received a single, subcutaneous (SC) dose of ION904 (or placebo) at day 1, then followed for 13 weeks. The primary objective was to assess safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of subcutaneously administered ION904. Plasma AGT protein levels over time were also measured. Other objectives were to evaluate the effects of ION904 on aldosterone, angiotensin II, plasma renin activity (PRA), renin mass, NT-pro B-type natriuretic peptide (BNP), and urinary angiotensinogen, and to assess potential pharmacokinetic/pharmacodynamic correlations on relevant biomarkers.

[0621] Laboratory Parameters

[0622] Chemistry and hematology parameters were measured by an automatic analyzer.

Angiotensinogen and exploratory RAAS metabolites aldosterone, angiotensin I, and angiotensin II were measured at Attoquant Diagnostics GmbH (Wien Austria). The angiotensinogen method utilized lithium-heparin plasma samples after full conversion of angiotensinogen with excess renin after a 60-minute incubation. The concentration of angiotensin I was measured by LC-MS/MS analysis using stable isotope labeled angiotensin I for internal standardization. Since it was assumed

that the conversion is 100% and there is a 1:1 molar relationship of angiotensin I to angiotensinogen, the angiotensin I concentration was equivalent to the angiotensinogen concentration. The lower limit of quantification, 2 nmol/L, was determined by the signal-to-noise ratio >10 of angiotensin I. The upper limit of quantification was 1975 nmol/L. Quality control (QC) samples were prepared using human angiotensinogen (IBL, Gunma, Japan) and were compared by cross-batch validation. In order to ensure that the entire angiotensinogen was metabolized by recombinant renin during the incubation period (60 min), the physiological concentration of human angiotensinogen (50 µg/ml) was spiked to surrogate sample matrix and incubated for 60 min, 120 min, and 180 min in independent technical replicates (triplicates). The measured angiotensinogen concentration following 120- and 180-min incubation did not exceed the measured concentration following 60-min incubation by >5%. Plasma renin activity was measured as the rate of formation of angiotensin I at 37 °C detected by LC-MS/MS in serum samples after incubation with renin (Attoquant Diagnostics). Angiotensin II and aldosterone were measured at Attoquant Diagnostics using similar LC/MS-MS using a stable isotope labelled internal standards for angiotensin II and aldosterone. Plasma renin mass and BNP levels were analyzed with established assays at Medpace Reference Laboratories (Cincinnati, OH).

[0623] Angiotensinogen was also measured at MedPace Reference Laboratories (MRL, Cincinnati, Ohio, U.S.A.) using an enzyme-linked immunoassay. Angiotensinogen levels of EDTA-plasma samples were detected with horse radish peroxidase mouse anti-human AGT monoclonal Fab' fragment (IBL-America).

[0624] Statistical Analysis

[0625] The safety set included all participants who were randomized and received at least 1 dose of ION904. The per protocol set included all participants who were randomized and received the protocol-specified ION904 drug exposure. The pharmacodynamics analysis was conducted in the per protocol set. The change and percent change from baseline in angiotensinogen and other parameters were summarized and compared between ION904 treatments and pooled placebo using 1-way analysis of variance (ANOVA) or, if data departed substantially from a normal distribution, the Wilcoxon Rank Sum test. The normality was tested by applying Kolmogorov-Smirnov test on the residuals at the 0.05 significance level.

[0626] Results**[0627] Demographic and Baseline Characteristics**

[0628] Subjects ranged in age from 18 to 62 years (mean = 46 years). 62.5% of subjects were male and 37.5% were female. The majority of subjects were White and not Hispanic or Latino (72.5%), 10.0% of subjects were black, and 17.5% of subjects were Asian. Body mass index (BMI) ranged from 20.1 5 kg/m² to 33.5 kg/m² (mean = 27.7 kg/m²).

[0629] Safety and Tolerability

[0630] Single ascending doses of ION904 were well tolerated with no drug related SAEs, no AE signals, no clinically meaningful changes in laboratory assessments, no hypotensive events, no acute renal changes or changes in renal function, no clinically relevant hyperkalemia, and no thrombocytopenia. There were no clinically relevant changes in chemistry, hematology, coagulation, urinalysis, or vital signs. Results of liver chemistry analyses demonstrated mild, transient alanine transaminase (ALT) elevations within the first 29 days of the study that were not clinically meaningful (< 3X upper limit of normal (ULN)).

[0631] Changes in Angiotensinogen Levels

[0632] The mean baseline plasma AGT levels were similar across the treatment groups. Single doses of ION904 resulted in significant and dose-dependent reductions in plasma AGT levels compared to placebo, with the largest reductions that were statistically significant ($p \leq 0.001$) in mean change and mean percent change in AGT reductions at days 15-29 (see FIG. 1 and Tables 7-10; all values based on analysis of a per protocol population of n=40). The maximum mean percent reduction ranged from 63% to 75% on day 15 through day 29 in the 60 mg, 90 mg, and 120 mg dose groups. At day 15 of the study, a significant mean percent reduction in plasma AGT protein levels as compared to pooled placebo saline (PBO) was observed (-3.3% (PBO) v. -75.2% (120 mg ION904) $p \leq 0.001$; see Tables 9 and 10) based on the AGT protein levels in plasma as determined at Attoquant Diagnostics GmbH, or (-12.3 % (PBO) v. -76.4 % (120 mg ION904) $p \leq 0.001$) based on AGT protein levels in plasma as determined by Medpace Reference Laboratories (Cincinnati, Ohio, U.S.A.). At day 15 of the study, single doses of 60 mg, 90 mg, and 120 mg of ION904 demonstrated up to about a 80% reduction in plasma AGT protein (see FIG. 1 and Tables 7-10; all values based on analysis of a per protocol population of n=40). The mean change and mean percent change in AGT reductions were robust, sustained, and significant at the higher doses (60 mg, 90 mg, and 120 mg) at most visits in the 3-month post-treatment period. Additionally, evidence of RAAS suppression was

observed as decreases in AngI and AngII were observed at day 29 (Tables 11 and 12; values based on analysis of a per protocol population of n=40) following single dose administration of ION904. Further support of RAAS suppression was observed as aldosterone was also decreased at day 29 following single dose administration of ION904, while placebo control subjects yielded increases in aldosterone levels.

[0633] Table 7: AGT protein levels in plasma of healthy subjects over time for placebo-treated, 10 mg ION904-treated, and 30 mg ION904-treated subjects.

Time Point	Subject Group – Plasma Angiotensinogen (nmol/L)		
	Placebo	ION904 10 mg	ION904 30 mg
Baseline	(n=10)	(n=6)	(n=6)
Mean	1111.7 (244.6, 77.3) ^a	1110.6 (435.1, 177.6) ^a	873.9 (80.9, 33.0) ^a
Median	1071.1 (951.7, 1303.3) ^b	901.6 (819.4, 1316.6) ^b	882.0 (800.9, 938.2) ^b
min/max	707.8/1535.2	813.6/1910.5	774.3/966.2
P-value ^c		0.993	0.067
Day 4	(n=10)	(n=6)	(n=6)
Mean	1055.9 (209.8, 66.3) ^a	1034.4 (365.0, 149.0) ^a	756.3 (115.1, 47.0) ^a
Median	1023.1 (907.4, 1175.7) ^b	890.6 (845.8, 1153.1) ^b	734.7 (660.9, 827.2) ^b
min/max	735.4/1403.7	707.8/1718.7	639.5/940.8
P-value ^c		0.834	0.006
Day 8	(n=10)	(n=6)	(n=6)
Mean	995.6 (280.2, 88.6) ^a	936.9 (340.3, 138.9) ^a	561.1 (154.7, 63.1) ^a
Median	998.2 (795.5, 1080.0) ^b	782.8 (753.3, 952.6) ^b	504.5 (453.8, 645.5) ^b
min/max	546.3/1463.0	737.3/1612.9	426.3/831.8
P-value ^d		0.429	0.014
Day 15	(n=10)	(n=6)	(n=6)
Mean	1066.5 (216.3, 68.4) ^a	836.9 (431.0, 176.0) ^a	498.5 (225.3, 92.0) ^a
Median	1015.8 (943.0, 1213.5) ^b	726.1 (633.7, 786.3) ^b	435.5 (332.7, 553.3) ^b
min/max	770.5/1495.1	463.6/1685.4	323.0/911.3
P-value ^d		0.063	0.009

Time Point	Subject Group – Plasma Angiotensinogen (nmol/L)		
	Placebo	ION904 10 mg	ION904 30 mg
Day 22	(n=9)	(n=6)	(n=6)
Mean	1183.3	904.6	516.9
	(298.9, 99.6) ^a	(342.2, 139.7) ^a	(201.1, 82.1) ^a
Median	1103.8	800.9	462.6
	(1051.5, 1246.0) ^b	(775.4, 838.1) ^b	(367.3, 597.4) ^b
min/max	701.2/1741.2	625.8/1586.7	342.9/868.4
P-value ^e		0.088	<0.001
Day 29	(n=10)	(n=6)	(n=6)
Mean	1103.3	845.9	535.7
	(248.2, 78.5) ^a	(288.9, 117.9) ^a	(217.2, 88.7) ^a
Median	1068.8	785.3	470.8
	(973.4, 1220.1) ^b	(734.7, 818.8) ^b	(371.8, 632.6) ^b
min/max	686.7/1616.9	549.7/1401.8	355.4/912.8
P-value ^d		0.094	0.007
Day 43	(n=10)	(n=6)	(n=6)
Mean	1092.7	856.5	598.4
	(252.1, 79.7) ^a	(442.8, 180.8) ^a	(190.5, 77.8) ^a
Median	1041.8	699.4	569.6
	(934.1, 1285.2) ^b	(615.9, 802.2) ^b	(463.5, 669.6) ^b
min/max	677.7/1484.4	580.9/1741.2	393.0/925.1
P-value ^d		0.077	0.007
Day 57	(n=10)	(n=6)	(n=6)
Mean	1068.5	975.7	647.0
	(276.6, 87.5) ^a	(310.5, 126.7) ^a	(160.0, 65.3) ^a
Median	1040.9	884.2	600.7
	(885.6, 1302.9) ^b	(830.3, 919.4) ^b	(508.9, 820.2) ^b
min/max	660.4/1580.0	739.7/1596.3	490.2/861.0
P-value ^d		0.371	0.014
Day 71	(n=10)	(n=5)	(n=6)
Mean	1082.6	850.6	700.9
	(242.3, 76.6) ^a	(142.6, 63.8) ^a	(128.9, 52.6) ^a
Median	1035.7	915.8	672.9
	(946.6, 1218.3) ^b	(775.8, 955.4) ^b	(597.6, 837.8) ^b
min/max	726.7/1568.9	635.7/970.1	561.5/862.9
P-value ^c		0.027	<0.001
Day 85	(n=10)	(n=6)	(n=6)
Mean	1073.1	1086.2	776.9
	(213.1, 67.4) ^a	(523.1, 213.5) ^a	(171.1, 69.8) ^a
Median	1065.9	896.8	739.2
	(1024.9, 1266.3) ^b	(800.0, 1330.6) ^b	(625.7, 892.2) ^b
min/max	605.2/1365.3	567.3/2025.8	610.7/1054.1
P-value ^c		0.928	0.047

^a(SD, SEM), ^b(P25, P75), ^cP-value of one-way ANOVA with treatment, ^d Wilcoxon rank sum test approximation two-sided P-value, ^e Wilcoxon rank sum exact test two-sided P-value

[0634] Table 8: AGT protein levels in plasma of healthy subjects over time for 60 mg ION904-treated, 90 mg ION904-treated, and 120 mg ION904-treated subjects.

Time Point	Subject Group – Plasma Angiotensinogen (nmol/L)		
	ION904 60 mg	ION904 90 mg	ION904 120 mg
Baseline	(n=6)	(n=6)	(n=6)
Mean	1035.1	931.4	1064.2
	(137.2, 56.0) ^a	(160.3, 65.5) ^a	(232.3, 94.8) ^a
Median	1037.3	905.9	1133.5
	(932.3, 1147.8) ^b	(869.5, 1016.1) ^b	(814.3, 1234.4) ^b
min/max	857.5/1198.4	704.9/1186.1	761.9/1307.4
P-value ^c	0.546	0.160	0.707
Day 4	(n=6)	(n=6)	(n=6)
Mean	784.8	603.0	640.9
	(147.4, 60.2) ^a	(97.1, 39.6) ^a	(87.5, 35.7) ^a
Median	761.2	574.9	653.1
	(681.2, 942.4) ^b	(543.5, 635.9) ^b	(561.0, 698.8) ^b
min/max	591.8/971.1	507.6/781.1	521.8/757.8
P-value ^c	0.012	<0.001	<0.001
Day 8	(n=6)	(n=6)	(n=6)
Mean	655.7	334.2	358.7
	(362.1, 147.8) ^a	(114.5, 46.8) ^a	(48.0, 19.6) ^a
Median	512.7	313.9	349.4
	(357.5, 1063.6) ^b	(250.5, 405.6) ^b	(326.5, 406.1) ^b
min/max	347.3/1140.8	205.1/516.4	299.0/421.7
P-value ^d	0.137	0.006	0.006
Day 15	(n=6)	(n=6)	(n=5)
Mean	340.2	238.7	273.9
	(147.3, 60.2) ^a	(130.7, 53.4) ^a	(56.3, 25.2) ^a
Median	306.9	213.8	248.1
	(246.8, 461.1) ^b	(121.5, 332.3) ^b	(247.0, 325.9) ^b
min/max	157.5/562.2	117.7/433.3	208.8/339.7
P-value ^d	0.006	0.006	0.010
Day 22	(n=6)	(n=6)	(n=6)
Mean	340.1	277.6	302.2
	(119.9, 48.9) ^a	(170.7, 69.7) ^a	(56.8, 23.2) ^a
Median	320.1	239.3	306.1
	(270.9, 446.4) ^b	(120.2, 416.9) ^b	(251.1, 346.5) ^b
min/max	175.8/507.3	120.1/530.1	235.3/367.9
P-value ^e	<0.001	<0.001	<0.001

Time Point	Subject Group – Plasma Angiotensinogen (nmol/L)		
	ION904 60 mg	ION904 90 mg	ION904 120 mg
Day 29	(n=6)	(n=6)	(n=6)
Mean	373.9	285.6	320.8
	(120.1, 49.0) ^a	(150.2, 61.3) ^a	(76.2, 31.1) ^a
Median	357.7	271.8	305.5
	(304.7, 454.1) ^b	(158.9, 377.1) ^b	(274.3, 333.1) ^b
min/max	211.4/557.9	136.3/497.9	245.7/460.4
P-value ^d	0.006	0.006	0.006
Day 43	(n=6)	(n=6)	(n=6)
Mean	522.3	372.2	478.9
	(161.6, 66.0) ^a	(203.1, 82.9) ^a	(168.8, 68.9) ^a
Median	485.9	322.8	419.9
	(417.2, 647.7) ^b	(219.3, 411.7) ^b	(334.4, 678.3) ^b
min/max	325.6/771.7	209.4/747.3	326.4/694.3
P-value ^d	0.007	0.007	0.009
Day 57	(n=6)	(n=6)	(n=6)
Mean	541.7	414.5	512.9
	(160.9, 65.7) ^a	(210.9, 86.1) ^a	(132.1, 53.9) ^a
Median	491.9	346.5	483.7
	(454.0, 710.1) ^b	(234.2, 608.1) ^b	(411.2, 635.8) ^b
min/max	341.5/760.7	230.5/721.3	359.5/703.8
P-value ^d	0.009	0.007	0.007
Day 71	(n=6)	(n=6)	(n=6)
Mean	618.7	480.7	607.7
	(121.8, 49.7) ^a	(217.7, 88.9) ^a	(145.0, 59.2) ^a
Median	591.1	405.3	562.1
	(559.8, 746.8) ^b	(312.9, 590.1) ^b	(523.5, 744.0) ^b
min/max	449.6/774.0	306.8/863.6	437.1/817.4
P-value ^c	<0.001	<0.001	<0.001
Day 85	(n=6)	(n=6)	(n=6)
Mean	846.2	544.4	709.2
	(267.9, 109.4) ^a	(190.2, 77.6) ^a	(183.2, 74.8) ^a
Median	697.2	436.5	697.2
	(689.1, 980.8) ^b	(432.0, 775.8) ^b	(526.3, 877.2) ^b
min/max	674.8/1338.4	384.4/800.9	514.8/942.8
P-value ^c	0.123	<0.001	0.016

^a(SD, SEM), ^b(P25, P75), ^cP-value of one-way ANOVA with treatment, ^d Wilcoxon rank sum test approximation test two-sided P-value, ^e Wilcoxon rank sum exact test two-sided P-value

[0635] Table 9: Percent change in plasma AGT protein levels of healthy subjects over time for placebo-treated, 10 mg ION904-treated, and 30 mg ION904-treated subjects.

Time Point	Subject Group – Percent Change in Plasma Angiotensinogen from Baseline		
	Placebo	ION904 10 mg	ION904 30 mg
Day 4	(n=10)	(n=6)	(n=6)
Mean	-4.0 (10.8, 3.4) ^a	-5.6 (8.5, 3.5) ^a	-13.4 (10.8, 4.4) ^a
Median	-5.2 (-15.5, 3.7) ^b	-7.7 (-12.4, -1.5) ^b	-14.3 (-23.3, -2.6) ^b
min/max	-16.6/17.0	-13.6/9.1	-26.2/0.3
P-value ^c		0.761	0.086
Day 8	(n=10)	(n=6)	(n=6)
Mean	-10.5 (14.9, 4.7) ^a	-13.3 (15.9, 6.5) ^a	-36.0 (15.1, 6.2) ^a
Median	-5.8 (-19.0, -2.7) ^b	-7.1 (-15.6, -6.5) ^b	-37.6 (-48.8, -29.7) ^b
min/max	-42.6/8.0	-44.0/0.8	-51.6/-10.6
P-value ^c		0.758	0.006
Day 15	(n=10)	(n=6)	(n=6)
Mean	-3.3 (8.3, 2.6) ^a	-23.5 (21.7, 8.8) ^a	-43.3 (23.4, 9.5) ^a
Median	-4.6 (-8.4, 5.9) ^b	-17.4 (-25.7, -11.8) ^b	-50.6 (-61.2, -32.9) ^b
min/max	-16.5/8.9	-64.8/-4.0	-62.6/-2.1
P-value ^c		0.019	<0.001
Day 22	(n=9)	(n=6)	(n=6)
Mean	8.5 (7.8, 2.6) ^a	-16.8 (14.5, 5.9) ^a	-41.2 (20.7, 8.5) ^a
Median	9.8 (-0.1, 14.4) ^b	-16.1 (-23.1, -2.4) ^b	-46.2 (-58.9, -29.6) ^b
min/max	-0.9/19.2	-41.1/-2.3	-59.5/-6.7
P-value ^d		<0.001	<0.001
Day 29	(n=10)	(n=6)	(n=6)
Mean	-0.5 (7.9, 2.5) ^a	-21.5 (15.5, 6.3) ^a	-39.1 (22.3, 9.1) ^a
Median	1.9 (-8.5, 5.3) ^b	-20.0 (-32.4, -8.6) ^b	-45.0 (-55.6, -27.5) ^b
min/max	-12.9/11.1	-44.2/-4.1	-59.5/-1.9
P-value ^c		0.009	<0.001
Day 43	(n=10)	(n=6)	(n=6)
Mean	-1.6 (7.2, 2.3) ^a	-22.9 (17.8, 7.3) ^a	-31.7 (19.6, 8.0) ^a
Median	-2.8 (-4.4, 0.8) ^b	-20.7 (-24.8, -8.9) ^b	-34.9 (-50.6, -18.5) ^b
min/max	-13.5/13.9	-55.9/-6.5	-50.9/-0.6
P-value ^c		0.023	0.002
Day 57	(n=10)	(n=6)	(n=6)
Mean	-4.4 (6.9, 2.2) ^a	-9.3 (14.9, 6.1) ^a	-26.2 (15.3, 6.2) ^a
Median	-2.5 (-9.2, 2.0) ^b	-7.8 (-16.4, -3.3) ^b	-25.0 (-38.8, -15.1) ^b
min/max	-15.3/4.2	-32.7/12.2	-45.8/-7.5
P-value ^c		0.549	0.012
Day 71	(n=10)	(n=5)	(n=6)
Mean	-2.3 (7.1, 2.2) ^a	-8.9 (17.0, 7.6) ^a	-19.8 (12.5, 5.1) ^a
Median	-3.5 (-8.6, 2.2) ^b	-9.6 (-21.9, -3.1) ^b	-20.8 (-29.9, -7.3) ^b
min/max	-9.8/12.7	-26.3/16.6	-34.3/-5.8
P-value ^c		0.448	0.036

Time Point	Subject Group – Percent Change in Plasma Angiotensinogen from Baseline		
	Placebo	ION904 10 mg	ION904 30 mg
Day 85	(n=10)	(n=6)	(n=6)
Mean	-2.8 (11.0, 3.5) ^a	-4.1 (16.0, 6.5) ^a	-11.2 (16.2, 6.6) ^a
Median	-3.3 (-12.0, 4.8) ^b	0.7 (-15.3, 6.0) ^b	-8.6 (-21.9, -6.7) ^b
min/max	-17.5/19.2	-30.3/13.7	-34.9/13.3
P-value ^c		0.896	0.393

^a(SD, SEM), ^b(P25, P75), ^cP-value of one-way ANOVA with treatment, ^d Wilcoxon rank sum exact test two-sided P-value

[0636] Table 10: Percent change in plasma AGT protein levels of healthy subjects over time for 60 mg ION904-treated, 90 mg ION904-treated, and 120 mg ION904-treated subjects.

Time Point	Subject Group – Percent Change in Plasma Angiotensinogen from Baseline		
	ION904 60 mg	ION904 90 mg	ION904 120 mg
Day 4	(n=6)	(n=6)	(n=6)
Mean	-24.5 (6.8, 2.8) ^a	-34.0 (13.0, 5.3) ^a	-38.3 (10.1, 4.1) ^a
Median	-23.9 (-31.0, -18.2) ^b	-35.3 (-40.3, -28.0) ^b	-39.5 (-48.2, -27.0) ^b
min/max	-31.9/-17.9	-52.1/-13.3	-49.0/-26.4
P-value ^c	<0.001	<0.001	<0.001
Day 8	(n=6)	(n=6)	(n=6)
Mean	-38.3 (27.9, 11.4) ^a	-62.6 (15.7, 6.4) ^a	-65.3 (6.6, 2.7) ^a
Median	-43.2 (-62.7, -7.3) ^b	-63.1 (-77.5, -50.2) ^b	-64.5 (-72.1, -60.9) ^b
min/max	-68.9/-4.8	-78.9/-42.7	-73.5/-56.2
P-value ^c	0.003	<0.001	<0.001
Day 15	(n=6)	(n=6)	(n=5)
Mean	-66.6 (15.4, 6.3) ^a	-72.7 (16.6, 6.8) ^a	-75.2 (5.6, 2.5) ^a
Median	-70.3 (-72.2, -61.5) ^b	-73.7 (-87.1, -60.1) ^b	-74.4 (-79.9, -73.5) ^b
min/max	-85.9/-39.7	-89.8/-51.9	-81.1/-67.3
P-value ^c	<0.001	<0.001	<0.001
Day 22	(n=6)	(n=6)	(n=6)
Mean	-66.6 (12.7, 5.2) ^a	-68.2 (20.9, 8.5) ^a	-70.1 (10.3, 4.2) ^a
Median	-67.5 (-72.1, -62.8) ^b	-69.7 (-86.8, -52.1) ^b	-71.5 (-79.4, -66.9) ^b
min/max	-84.3/-45.6	-89.9/-41.1	-79.7/-51.7
P-value ^d	<0.001	<0.001	<0.001
Day 29	(n=6)	(n=6)	(n=6)
Mean	-63.2 (13.3, 5.4) ^a	-67.2 (19.9, 8.1) ^a	-68.9 (8.5, 3.5) ^a
Median	-63.9 (-68.3, -62.1) ^b	-70.5 (-85.0, -47.0) ^b	-68.9 (-77.2, -62.5) ^b
min/max	-81.1/-40.2	-85.6/-44.7	-79.0/-56.8
P-value ^c	<0.001	<0.001	<0.001

Time Point	Subject Group – Percent Change in Plasma Angiotensinogen from Baseline		
	ION904 60 mg	ION904 90 mg	ION904 120 mg
Day 43	(n=6)	(n=6)	(n=6)
Mean	-48.6 (18.1, 7.4) ^a	-57.9 (24.9, 10.2) ^a	-53.4 (17.3, 7.1) ^a
Median	-51.2 (-56.7, -44.6) ^b	-62.3 (-79.4, -44.6) ^b	-51.9 (-71.8, -38.1) ^b
min/max	-70.8/-17.2	-81.5/-17.0	-73.6/-33.1
P-value ^c	<0.001	<0.001	<0.001
Day 57	(n=6)	(n=6)	(n=6)
Mean	-46.9 (17.2, 7.0) ^a	-53.0 (26.5, 10.8) ^a	-50.6 (12.8, 5.2) ^a
Median	-47.2 (-58.3, -40.7) ^b	-56.4 (-74.5, -30.1) ^b	-49.3 (-60.2, -38.7) ^b
min/max	-69.4/-18.4	-80.6/-19.9	-68.5/-37.5
P-value ^c	<0.001	<0.001	<0.001
Day 71	(n=6)	(n=6)	(n=6)
Mean	-39.3 (14.2, 5.8) ^a	-46.0 (27.2, 11.1) ^a	-41.7 (12.9, 5.3) ^a
Median	-36.6 (-51.2, -31.6) ^b	-49.4 (-69.8, -32.1) ^b	-39.9 (-51.8, -30.5) ^b
min/max	-59.7/-19.9	-71.3/-4.1	-60.0/-28.3
P-value ^c	<0.001	<0.001	<0.001
Day 85	(n=6)	(n=6)	(n=6)
Mean	-16.7 (31.1, 12.7) ^a	-39.7 (23.9, 9.7) ^a	-32.7 (12.8, 5.2) ^a
Median	-22.9 (-38.3, -18.2) ^b	-47.6 (-57.8, -11.1) ^b	-33.9 (-36.9, -23.3) ^b
min/max	-41.2/43.6	-63.6/-10.8	-53.0/-15.5
P-value ^c	0.164	<0.001	0.004

^a(SD, SEM), ^b(P25, P75), ^cP-value of one-way ANOVA with treatment, ^d Wilcoxon rank sum exact test two-sided P-value

[0637] Table 11: Serum AngI and Ang II and change in levels from baseline in healthy subjects at Day 29 for placebo-treated, 10 mg ION904-treated, and 30 mg ION904-treated subjects.

Time Point	Subject Group – Serum Ang I and Ang II Levels and Changes		
	Placebo (n=10)	ION904 10 mg (n=6)	ION904 30 mg (n=6)
Angiotensin I (pmol/L)			
Baseline			
Mean	17.9 (7.3, 2.3) ^a	48.4 (58.9, 24.0) ^a	23.4 (18.9, 7.7) ^a
Median	20.6 (9.8, 22.9) ^b	28.7 (17.7, 33.9) ^b	19.7 (9.4, 28.4) ^b
min/max	7.4 /26.6	13.7/167.4	5.6/57.5
P-value ^c		0.137	0.790

Time Point	Subject Group – Serum Ang I and Ang II Levels and Changes		
	Placebo (n=10)	ION904 10 mg (n=6)	ION904 30 mg (n=6)
Day 29			
Mean	28.4 (17.3, 5.5) ^a	22.2 (11.0, 4.5) ^a	28.7 (15.4, 6.3) ^a
Median	29.3 (17.1, 34.5) ^b	22.2 (12.9, 27.6) ^b	28.4 (22.3, 41.2) ^b
min/max	7.3/68.0	9.4/38.9	3.9/48.2
P-value ^d		0.353	0.957
Change Day 29 - Baseline			
Mean	10.5 (17.2, 5.4) ^a	-26.2 (57.8, 23.6) ^a	5.4 (10.1, 4.1) ^a
Median	5.5 (-0.3, 11.5) ^b	-10.8 (-24.0, 13.5) ^b	5.8 (1.7, 12.8) ^b
min/max	-5.8/52.2	-139.8/14.9	-9.3/18.7
P-value ^c		0.195	0.873
%Change Day 29 - Baseline			
Mean	79.7 (143.5, 45.4) ^a	-11.9 (74.9, 30.6) ^a	44.8 (82.8, 33.8) ^a
Median	22.5 (-3.9, 53.2) ^b	-38.2 (-71.9, 62.1) ^b	29.3 (-16.2, 58.2) ^b
min/max	-25.3/366.2	-83.5/98.5	-30.4/198.9
P-value ^c		0.164	0.873
Angiotensin II (pmol/L)			
Baseline			
Mean	77.4 (35.3, 11.2) ^a	106.4 (45.8, 18.7) ^a	104.4 (71.0, 29.0) ^a
Median	72.8 (53.0, 109.0) ^b	103.4 (90.7, 125.2) ^b	82.6 (52.8, 171.1) ^b
min/max	27.5/123.2	38.0/178.0	29.2/208.1
P-value ^d		0.286	0.320
Day 29			
Mean	109.0 (45.9, 14.5) ^a	95.2 (43.6, 17.8) ^a	126.6 (95.8, 39.1) ^a
Median	112.0 (77.5, 144.4) ^b	85.1 (71.4, 133.1) ^b	118.3 (55.4, 171.1) ^b
min/max	34.0/167.1	38.2/158.3	14.1/282.2
P-value ^d		0.643	0.555
Change Day 29 - Baseline			
Mean	31.6 (36.0, 11.4) ^a	-11.2 (72.4, 29.5) ^a	22.2 (65.9, 26.9) ^a
Median	28.3 (4.4, 50.0) ^b	-1.1 (-87.0, 52.0) ^b	36.1 (-15.1, 74.1) ^b
min/max	-4.7/114.1	-97.8/67.6	-83.0/84.9
P-value ^d		0.154	0.751
%Change Day 29 - Baseline			
Mean	56.0 (79.6, 25.2) ^a	14.7 (81.5, 33.3) ^a	23.7 (71.3, 29.1) ^a
Median	25.3 (4.9, 70.7) ^b	0.5 (-54.9, 74.5) ^b	20.3 (-48.5, 68.4) ^b
min/max	-12.1/215.3	-69.5/136.8	-51.7/133.5
P-value ^c		0.429	0.560

^a(SD, SEM), ^b(P25, P75), ^c Wilcoxon rank sum t approximation test two-sided P-value, ^dP-value of one-way ANOVA with treatment

[0638] Table 12: Serum AngI and Ang II and change in levels from baseline in healthy subjects at Day 29 for 60 mg ION904-treated, 90 mg ION904-treated, and 120 mg ION904-treated subjects.

Time Point	Subject Group – Serum Ang I and Ang II Levels and Changes		
	ION904 60 mg (n=6)	ION904 90 mg (n=6)	ION904 120 mg (n=6)
Angiotensin I (pmol/L)			
Baseline			
Mean	11.8 (7.2, 2.9) ^a	25.8 (17.6, 7.2) ^a	20.8 (7.0, 2.9) ^a
Median	7.7 (7.3, 19.1) ^b	24.9 (12.1, 36.7) ^b	20.0 (17.8, 22.2) ^b
min/max	6.3/ 22.7	4.2 - 51.9	11.9 /33.1
P-value ^c	0.103	0.492	0.790
Day 29			
Mean	15.1 (5.4, 2.2) ^a	15.6 (9.4, 3.9) ^a	17.5 (9.1, 3.7) ^a
Median	13.5 (11.4, 16.0) ^b	16.4 (5.7, 20.7) ^b	14.2 (10.2, 24.5) ^b
min/max	10.7/25.3	5.3/29.1	10.0/31.9
P-value ^d	0.051	0.060	0.106
Change Day 29 - Baseline			
Mean	3.3 (3.4, 1.4) ^a	-10.2 (21.3, 8.7) ^a	-3.3 (8.7, 3.5) ^a
Median	4.2 (2.6, 4.6) ^b	-8.4 (-16.4, 1.5) ^b	-5.4 (-9.0, -1.2) ^b
min/max	-3.1/7.1	-46.6/17.0	-11.6/12.6
P-value ^c	0.670	0.063	0.052
%Change Day 29 - Baseline			
Mean	45.1 (39.5, 16.1) ^a	-4.1 (81.5, 33.3) ^a	-9.2 (59.6, 24.3) ^a
Median	58.5 (11.5, 69.8) ^b	-33.3 (-44.7, 35.7) ^b	-29.0 (-47.4, -3.6) ^b
min/max	-16.2/88.8	-89.8-140.5	-52.3/105.9
P-value ^c	0.492	0.137	0.077
Angiotensin II (pmol/L)			
Baseline			
Mean	61.5 (42.8, 17.5) ^a	98.8 (55.9, 22.8) ^a	98.9 (62.4, 25.5) ^a
Median	36.1 (35.6, 114.2) ^b	97.3 (59.7, 128.0) ^b	76.6 (58.5, 135.9) ^b
min/max	28.1/119.1	24.4/186.4	38.5/207.1
P-value ^d	0.555	0.429	0.429
Day 29			
Mean	68.8 (44.0, 18.0) ^a	60.2 (36.5, 14.9) ^a	85.6 (63.4, 25.9) ^a
Median	51.9 (44.8, 65.8) ^b	60.5 (24.4, 69.3) ^b	79.9 (25.4, 146.8) ^b
min/max	41.4/156.9	23.6/123.2	22.2/159.5
P-value ^d	0.181	0.107	0.433

Time Point	Subject Group – Serum Ang I and Ang II Levels and Changes		
	ION904 60 mg (n=6)	ION904 90 mg (n=6)	ION904 120 mg (n=6)
Change Day 29 - Baseline			
Mean	7.3 (29.6, 12.1) ^a	-38.6 (74.5, 30.4) ^a	-13.3 (60.6, 24.7) ^a
Median	12.7 (5.6, 23.2) ^b	-36.8 (-58.7, 0.0) ^b	-24.7 (-45.0, 10.9) ^b
min/max	-48.4/37.8	-162.8/63.5	-87.2/91.2
P-value ^d	0.414	0.023	0.136
%Change Day 29 - Baseline			
Mean	26.3 (40.9, 16.7) ^a	-17.1 (66.6, 27.2) ^a	-8.8 (73.5, 30.0) ^a
Median	28.8 (15.6, 44.6) ^b	-37.8 (-45.9, 0.0) ^b	-42.2 (-53.1, 8.0) ^b
min/max	-42.4/82.6	-87.3/106.4	-56.6/133.5
P-value ^c	1.000	0.052	0.077

^a(SD, SEM), ^b(P25, P75), ^c Wilcoxon rank sum t approximation test two-sided P-value, ^dP-value of one-way ANOVA with treatment

[0639] Pharmacokinetics

[0640] ION904 was rapidly absorbed within a few hours following subcutaneous administration and exposure increased with dose in a dose-dependent manner across the studied dose range of 10 mg to 120 mg. Rapid clearance from plasma and yet limited recovery in urine (<1% of administered dose in 24 hours) suggests that clearance from plasma occurs primarily by distribution to tissues, where the compound is metabolized prior to renal excretion as metabolites (FIGS. 2 and 3). As shown in Table 13, the elimination half-life of ION904 in plasma was approximately 2 weeks to 3.5 weeks after a single subcutaneous dose, reflecting the long tissue half-life of ION904 and supportive of infrequent dosing. Intact fully conjugated ION904 was the most abundant circulating species in human plasma and accounted for 100% of total detected full-length oligonucleotides in the samples evaluated.

[0641] Table 13: Summary of Plasma Pharmacokinetic Parameters of ION904.

	Cohort @ Study Day 1 (Dose (mg))				
	A (10 mg)	B (30 mg)	C (60 mg)	D (90 mg)	E (120 mg)
N	6	6	6	6	6
C _{max} (ug/mL)	0.03 (57.9)	0.07 (30.1)	0.14 (42.1)	0.23 (41.0)	0.32 (33.2)
t _{max} (h)	2.00 (2.00, 8.00)	2.50 (2.00, 12.0)	9.00 (6.00, 12.1)	8.00 (6.00, 12.0)	7.00 (6.00, 12.0)
AUC _{0-24h} (ug*h/mL)	0.28 (20.2)	1.01 (26.3)	1.84 (22.9)	3.23 (34.3)	4.31 (21.0)

	Cohort @ Study Day 1 (Dose (mg))				
	A (10 mg)	B (30 mg)	C (60 mg)	D (90 mg)	E (120 mg)
AUC_{last}^a ($\mu g \cdot h/mL$)	0.32 (17.8)	1.22 (25.1)	2.56 (16.3)	4.31 (39.2)	5.49 (14.3)
$AUC_{0-\infty}$ ($\mu g \cdot h/mL$)	NC	1.15 (5.63) ^d	2.61 (18.3) ^e	4.40 (39.3)	5.68 (17.0) ^f
CL_{0-24h}/F^b (L/h)	36.1 (20.2)	29.7 (26.3)	32.6 (22.9)	27.9 (34.3)	27.8 (21.0)
CL/F^c (L/h)	NC	26.2 (5.63) ^d	23.0 (18.3) ^e	20.5 (39.3)	21.1 (17.0) ^f
V_z/F (L)	NC	11204 (20.4) ^d	15644 (25.1) ^e	16726 (32.9)	18604 (27.9) ^f
$t_{1/2\lambda z}$ (day)	NC	12.4 (14.9) ^d	19.7 (38.2) ^e	23.6 (23.6)	25.4 (20.4) ^f

Data presented are geometric mean (geometric %CV) except t_{max} , which is presented as median (minimum, maximum). Individual subject values for $t_{1/2\lambda z}$, $AUC_{0-\infty}$, CL/F , and V_z/F were not included in descriptive statistics if the r-square adjusted < 0.8, span < 1.5, or if there were less than three data points in the elimination phase because λz could not be accurately defined.

N = number of subjects

NC = not calculated

^a t_{last} = 24 to 2016 h

^b CL_{0-24h}/F = Actual Dose/ AUC_{0-24h}

^c CL/F = Actual Dose/ $AUC_{0-\infty}$

^d N = 3

^e N = 5

^f N = 4

[0642] The relationship between plasma angiotensinogen levels (% of baseline) and plasma concentrations on Day 29 following a single subcutaneous dose of ION904 was explored using an inhibitory maximum drug effect (E_{max}) model (FIG. 4). Day 29 was selected to represent C_{trough} (the time point at which plasma concentrations are expected to be in equilibrium with target tissue exposure) based on the monthly dosing regimen utilized in subsequent clinical studies. The estimated plasma concentration that produced 50% of maximum drug-induced effect (EC_{50}) was 0.13 ± 0.014 ng/mL (estimate $\pm$ standard error (SE)). There were no clinically relevant effects on heart rate or on

cardiac conduction (PR and QRS intervals) and based on the concentration-QTc analysis, an effect on $\Delta\Delta\text{QTcF}$ exceeding 10 ms can be excluded within the full observed range of plasma concentrations of ION904 up to $\sim 0.44 \mu\text{g/mL}$.

[0643] Changes in RAAS biomarkers and B-type Natriuretic Peptide

[0644] Plasma aldosterone levels were significantly reduced in the ION904 30 mg (-24.7%, $p=0.026$), 90 mg (-34.8%, $p=0.005$, and 120 mg dose (-30.4, $p=0.003$) cohorts at Day 22. Plasma Ang II was significantly reduced in the 30 mg (-0.5%, $p=0.033$) and 90 mg dose (-28.2%, $p=0.008$) cohorts at Day 22. Renin mass increased significantly in the 90 mg (400.4%, $p=0.05$) and 120 mg (290.9%, $p=0.012$) dose cohorts at Day 22. No significant changes were noted in plasma renin activity or BNP, as shown in Table 14.

[0645] Table 14: Effect of ION904 on RAAS metabolites and BNP.

Metabolite, mean % change from baseline at Day 22 (SD)	Placebo	ION904 10 mg	ION904 30 mg
Aldosterone P-Value*	11.3 (38.8)	13.7 (78.4) 0.776	-24.7 (20.5) 0.026
Angiotensin II P-Value*	28.6 (32.1)	4.9 (26.4) 0.235	-0.5 (16.4) 0.033
Renin Mass P-Value*	79.7 (80.0)	45.8 (104.8) 0.388	98.8 (99.0) 0.864
Renin Activity P-Value*	92.8 (115.9)	31.1 (101.8) 0.328	-11.6 (34.5) 0.05
BNP P-Value*	17.5 (51.2)	30.3 (73.1) 0.662	59.7 (115.3) 0.876
Metabolite, mean % change from baseline (SD)	ION904 60 mg	ION904 90 mg	ION904 120 mg
Aldosterone P-Value*	-7.8 (22.6) 0.328	-34.8 (13.4) 0.005	-30.4 (11.8) 0.003
Angiotensin II P-Value*	9.1 (20.8) 0.224	-28.2 (26.1) 0.008	2140 (1100) 0.026
Renin Mass P-Value*	168.7 (140.4) 0.181	400.4 (346.7) 0.050	290.9 (190.7) 0.012
Renin Activity P-Value*	71.4 (53.4) 0.955	-12.8 (37.4) 0.088	81.7 (109.2) 0.955
BNP P-Value*	-26.7 0.667	-10.4 (37.8) 0.345	-23.7 (35.3) 0.140

* P-value is from Wilcoxon rank sum exact two-sided test.

[0646] Results for ION904 thus demonstrated significant reductions in plasma AGT protein levels as well as evidence of RAAS suppression, with a favorable safety and tolerability profile. Notably, ION904 reductions were more potent and more durable as compared to ISIS 757456.

[0647] Example 3: Effects of ION904 in Subjects with Uncontrolled Hypertension

[0648] Study Design

[0649] A double-blind, randomized, placebo-controlled phase 2 study of monthly subcutaneous administration of ION904 (ClinicalTrials.gov Identifier NCT05314439) was conducted with subjects having uncontrolled hypertension to assess safety, tolerability, and efficacy of ION904. Forty-eight subjects with systolic blood pressure > 130 to ≤ 170 mmHg who had been on one or more antihypertensive medications for at least one month were randomized (3:1 randomization) to receive ION904 (30 mg, 60 mg, or 90 mg of ION904) or placebo (PBO) every 4 weeks (e.g., every 28 days) for 3 months. Patients were stratified based on baseline ACE inhibitor (ACEi)/angiotensin II receptor blocker (ARB) treatment (current use vs. no current use) and then randomized in parallel into one of the 3 cohorts to receive placebo or ION904 at 30 mg (Cohort A), 60 mg (Cohort B), or 90 mg (Cohort C) monthly with up to 4 subcutaneous doses. Within each cohort, patients were further randomized to receive either ION904 or placebo in a 3:1 ratio. All cohorts underwent up to a 4-week Screening Period and a 13-week Treatment Period, followed by a 13-week Post-Treatment Follow-up Period. All safety data including adverse events (AEs), blood pressure, and concomitant medications were reviewed by the Sponsor's Medical Monitor or designee on an ongoing basis throughout the trial. The Phase 2 study design is summarized in Table 15.

[0650] Table 15: Design of Phase 2 Study according to Example 3.

[0651] Period	Duration
Screening Period	4 weeks
<i>Eligible Patients Only</i>	
Treatment Period ¹	13 weeks
End of treatment (EOT) visit/Early termination from treatment ²	2 weeks after last dose
Post-Treatment Period	13 weeks
End of study (EOS) procedures/early termination from post-treatment ³	—

¹ Patients who early terminated from the Treatment Period entered the Post Treatment Period, starting with the EOT visit.

² Last visit for patients who withdrew consent during the Treatment Period.

³ Last visit for patients who withdrew consent or early terminated during the Post-Treatment Period.

[0652] The primary objective was to evaluate the effect of ION904 on plasma angiotensinogen in patients with uncontrolled hypertension. The primary endpoint was percent change in plasma angiotensinogen from Baseline to Study Day 99 in ION904-treated patients compared to placebo. The secondary objective was to evaluate the effect of ION904 on seated automated office systolic blood pressure (SBP) and diastolic blood pressure (DBP). The safety endpoints included incidence and severity of TEAEs, use of concomitant medications, abnormal findings in laboratory assessments, electrocardiogram, and vital signs. Additionally, incidence of hyperkalemia, hypotension, and renal dysfunction were assessed. Pharmacokinetic objectives evaluated the PK of ION904 (exposure in plasma) and potential pharmacokinetic/pharmacodynamic relationship with relevant biomarkers. Other objectives evaluated the effects of ION904 on plasma angiotensinogen, SBP, and DBP at each scheduled visit, angiotensin II, PRA, and renin mass.

[0653] Laboratory Parameters

[0654] Chemistry and hematology parameters were measured by an automatic analyzer. Angiotensinogen and exploratory RAAS metabolites aldosterone, angiotensin I, and angiotensin II were measured at Attoquant Diagnostics GmbH (Wien Austria). The angiotensinogen method utilized lithium-heparin plasma samples after full conversion of angiotensinogen with excess renin after a 60-minute incubation. The concentration of angiotensin I was measured by LC-MS/MS analysis using stable isotope labeled angiotensin I for internal standardization. Since it was assumed that the conversion is 100% and there is a 1:1 molar relationship of angiotensin I to angiotensinogen, the angiotensin I concentration was equivalent to the angiotensinogen concentration. The lower limit of quantification, 2 nmol/L, was determined by the signal-to-noise ratio >10 of angiotensin I. The upper limit of quantification was 1975 nmol/L. Quality control (QC) samples were prepared using human angiotensinogen (IBL, Gunma, Japan) and were compared by cross-batch validation. In order to ensure that the entire angiotensinogen was metabolized by recombinant renin during the incubation period (60 min), the physiological concentration of human angiotensinogen (50 µg/ml) was spiked to surrogate sample matrix and incubated for 60 min, 120 min, and 180 min in independent technical replicates (triplicates). The measured angiotensinogen concentration following 120- and 180-min incubation did not exceed the measured concentration following 60-min incubation by >5%. Plasma

renin activity was measured as the rate of formation of angiotensin I at 37 °C detected by LC-MS/MS in serum samples after incubation with renin (Attoquant Diagnostics).

[0655] Statistical Analysis

[0656] The data were analyzed using analysis of covariates (ANCOVA) model with treatment, baseline value, and randomization stratification factor (current use of ACEi/ARB vs. no current use of ACEi/ARB) as independent variables. Least square mean (LSM) difference with 95% confidence interval (CI) and p-values between each treatment group and the pooled placebo were provided based on the ANCOVA model. The normality assumption was assessed by the Shapiro-Wilk test based on the residuals from ANCOVA modeling. If data departed substantially from normality, the nonparametric van Elteren test was used instead, with treatment and randomization stratification factor (current use of ACEi/ARB vs. no current use of ACEi/ARB) as independent variables.

[0657] *Results*

[0658] Baseline Characteristics

[0659] Key baseline characteristics are summarized in Table 16. Conditions reported for at least 25% of patients were obesity (58.3% placebo, 52.8% ION904), type 2 diabetes mellitus (41.7% placebo, 41.7% ION904), dyslipidemia (16.7% placebo, 30.6% ION904), and depression (8.3% placebo, 27.8% ION904). The proportion of patients taking an ACEi or ARB at baseline was 66.7% for the placebo group and 61.1% for the ION904 group overall.

[0660] Table 16: Baseline Characteristics of participants in the Phase 2 Study.

Patient Characteristics	Placebo (N=12)	ION904 30 mg (N=11)	ION904 60 mg (N=13)	ION904 90 mg (N=12)
Age (years) (SD)	58.3 (9.3)	60.7 (10.1)	63.8 (6.5)	61.9 (7.6)
Male, N (%)	11 (91.7)	7 (63.6)	7 (53.8)	6 (50)
Female, N (%)	1 (8.3)	4 (36.4)	6 (46.2)	6 (50)
White, N (%)	7 (58.3)	9 (81.8)	7 (53.8)	10 (83.3)
BMI (kg/m ²) (SD)	31.6 (6.2)	32.5 (4.8)	31.8 (5.7)	29.1 (5.1)
Hyperlipidemia, N (%)	8 (66.7)	6 (54.5)	8 (61.5)	8 (66.7)
Type 2 Diabetes Mellitus, N (%)	5 (41.7)	5 (45.5)	6 (46.2)	4 (33.3)

Patient Characteristics	Placebo (N=12)	ION904 30 mg (N=11)	ION904 60 mg (N=13)	ION904 90 mg (N=12)
Angiotensinogen (nmol/L) (SD)	853 (161)	783 (212)	975 (277)	935 (178)
SBP Screening (mmHg) (SD)	145.2 (8.6)	142.5 (10.2)	146.2 (10.5)	144.8 (12.2)
DBP Screening (mmHg) (SD)	86.2 (11.5)	83.0 (14.1)	85.2 (10.6)	82.4 (13.6)
ACEi/ARB, N (%)	8 (66.7)	7 (63.6)	8 (61.5)	7 (58.3)
Creatinine (μmol/L) (SD)	75.3 (13.6)	77.9 (39.3)	76.7 (19.1)	82.9 (24.2)
eGFR (mL/min/1.73m ²) (SD)	97.2 (11.2)	95.3 (14.5)	85.9 (13.2)	86.0 (19.8)
Potassium (mmol/L) (SD)	4.43 (0.58)	4.48 (0.46)	4.15 (0.41)	4.18 (0.33)
Aldosterone (pmol/L) (SD)	162.5 (130.6)	205.87 (132.0)	148.08 (128.6)	269.92 (158.4)
Angiotensin II (pmol/L) (SD)	167.5 (127.8)	100.7 (189.2)	165.3 (225.8)	207.2 (302.7)
Renin Mass (pg/mL) (SD)	26.0 (31.9)	43.8 (38.3)	75.3 (90.0)	38.1 (41.0)
Plasma Renin Activity (pmol/L/min) (SD)	312 (406)	283 (262)	419 (381)	365 (409)

Continuous data is presented as mean (SD). The angiotensinogen baseline values were defined as the averaged values collected between Day -7 and prior to the first dose of placebo or ION904.

[0661] Including new initiation during the study, the use of ACEi or ARB was 75.0% for the placebo group and 80.6% for the ION904-treated group overall. Subjects maintained pre-existing (baseline) and initiated (after baseline) antihypertension medication regimen throughout the study (Table 17; full analysis set). The majority of subjects being treated with an ACEi or ARB were taking low doses (Tables 18 and 19).

[0662] Table 17: Hypertensive medication treatments of subjects with uncontrolled hypertension.

Existing Medication	Subject Group and Number of Subjects				
	Placebo (N=12)	ION904 30 mg (N=11)	ION904 60 mg (N=13)	ION904 90 mg (N=12)	ION904 Total (N=36)
ACEi	6 (50% of group)	8 (73% of group)	4 (31% of group)	5 (42% of group)	17 (47% of total)
ARB	3 (25% of group)	2 (18% of group)	6 (46% of group)	4 (33% of group)	12 (33% of total)
Calcium Channel Blocker	2 (17% of group)	2 (18% of group)	6 (46% of group)	6 (50% of group)	14 (39% of total)
Diuretic	6 (50% of group)	4 (46% of group)	5 (39% of group)	5 (42% of group)	15 (42% of total)
Beta-Blocker	4 (33% of group)	5 (46% of group)	3 (23% of group)	5 (42% of group)	13 (36% of total)
Vasodilator	1 (8% of group)	0	0	1 (8% of group)	1 (3% of total)
MRA	0	1 (1% of group)	0	0	1 (3% of total)

[0663] Table 18: Relative ACE inhibitor or ARB dose of subjects taking an ACEi or ARB.

	Subject Group and Number of Subjects				
	Placebo (N=12)	ION904 30 mg (N=11)	ION904 60 mg (N=13)	ION904 90 mg (N=12)	ION904 Total (N=36)
ACEi or ARB High Dose	0	3 (27.3%)	3 (23.1%)	2 (16.7%)	8 (22.2%)
ACEi or ARB Low Dose	9 (75.0%)	7 (63.6%)	7 (53.8%)	6 (50.0%)	20 (55.6%)
ACEi or ARB No Dose	3 (25.0%)	1 (9.1%)	3 (23.1%)	4 (33.3%)	8 (22.2%)

[0664] Table 19: ACE inhibitor and ARB dose stratum.

ACEi/ARB	Low Dose Stratum (total mg per day)	High Dose Stratum (total mg per day)
ACEi		

ACEi/ARB	Low Dose Stratum (total mg per day)	High Dose Stratum (total mg per day)
benazepril	≤ 20	> 20
captopril	≤ 75	> 75
enalapril	≤ 10	> 10
fosinopril	≤ 20	> 20
lisinopril	≤ 20	> 20
perinodpril	< 8	≥ 8
quinapril	< 40	≥ 40
ramipril	≤ 10	> 10
trandolapril	≤ 4	> 4
ARB		
azilsartan	≤ 40	> 40
candesartan	< 16	≥ 16
eprosartan	≤ 400	> 400
irbesartan	≤ 150	> 150
losartan	≤ 50	> 50
olmesartan	≤ 20	> 20
telmisartan	≤ 40	> 40
valsartan	≤ 160	> 160

[0665] Primary Endpoint: Plasma Angiotensinogen Levels

[0666] Dose-dependent reductions in plasma AGT protein were observed in all ION904 treated subjects at day 99 (week 15), with PBO group: -6% v. 30 mg cohort: -71%, 60 mg cohort: -70%, and 90 mg cohort: -79% reduction in mean plasma AGT protein compared to baseline level. See Tables 20 and 21 (values based on full analysis of a population of n=48), and FIG. 5 (values based on an analysis of a per protocol population of n=39). Robust median plasma AGT protein reductions were observed at the primary endpoint, as maximum median percent reduction of 86% in plasma AGT protein was achieved by day 99 after 4 doses of 90 mg of compound ION904; and a maximum median percent reduction of 79% in plasma AGT protein was achieved by day 99 after 4 doses of 60 mg of compound ION904 (see Tables 20 and 21, values based on full analysis of a population of n=48; and FIG. 6 values based on an analysis of a per protocol population of n=39).

[0667] Table 20: Plasma AGT protein levels of subjects with uncontrolled hypertension over time.

Time Point	Subject Group - Angiotensinogen (nmol/L)			
	Pooled Placebo	ION904 30 mg	ION904 60 mg	ION904 90 mg
Baseline				
Mean	(n=12) 853.43 (161.445, 46.605) ^a	(n=11) 783.31 (211.562, 63.788) ^a	(n=13) 975.25 (276.513, 76.691) ^a	(n=12) 935.84 (177.921, 51.361) ^a
Median	858.65 (727.73, 931.58) ^b	835.20 (669.35, 908.20) ^b	885.00 (830.65, 973.30) ^b	903.40 (790.20, 1073.93) ^b
min/max	608.0/1120.7	457.0/1170.9	665.6/1494.7	678.4/1236.4
Day 15				
Mean	(n=12) 763.73 (164.541, 47.499) ^a	(n=10) 370.59 (128.693, 40.696) ^a	(n=13) 379.79 (168.355, 46.693) ^a	(n=12) 262.93 (160.275, 46.267) ^a
Median	736.00 (627.50, 904.50) ^b	350.95 (310.60, 394.40) ^b	384.50 (245.90, 474.70) ^b	234.75 (138.75, 339.25) ^b
min/max	545.5/1021.5	165.0/589.4	163.3/696.0	91.3/618.2
Day 29				
Mean	(n=12) 767.56 (200.448, 57.864) ^a	(n=10) 387.12 (107.492, 33.992) ^a	(n=13) 374.18 (160.538, 44.525) ^a	(n=12) 288.08 (149.256, 43.087) ^a
Median	726.75 (603.05, 902.85) ^b	375.55 (307.80, 435.20) ^b	337.70 (217.80, 481.50) ^b	285.45 (178.60, 338.90) ^b
min/max	515.0/1216.5	253.7/573.7	171.4/684.7	120.4/676.8
Day 43				
Mean	(n=11) 836.55 (240.847, 72.618) ^a	(n=10) 290.45 (116.156, 36.732) ^a	(n=13) 285.57 (158.359, 43.921) ^a	(n=12) 214.43 (173.032, 49.950) ^a
Median	782.90 (615.80, 994.40) ^b	254.05 (197.50, 349.90) ^b	261.40 (154.60, 393.20) ^b	150.10 (124.55, 247.40) ^b
min/max	510.0/1279.6	178.7/500.2	93.8/583.2	81.0/715.1
Day 57				
Mean	(n=11) 795.73 (211.201, 63.679) ^a	(n=9) 300.94 (94.627, 31.542) ^a	(n=11) 343.67 (172.517, 52.016) ^a	(n=11) 245.45 (196.412, 59.221) ^a
Median	756.80 (656.70, 896.50) ^b	282.40 (237.80, 341.40) ^b	343.80 (201.50, 503.10) ^b	185.40 (130.90, 295.20) ^b
min/max	539.1/1316.3	195.7/453.1	147.7/677.9	91.7/798.1
Day 71				
Mean	(n=11) 769.14 (250.698, 75.588) ^a	(n=9) 242.98 (99.948, 33.316) ^a	(n=11) 294.15 (174.852, 52.720) ^a	(n=10) 218.87 (199.598, 63.119) ^a
Median	671.10 (562.50, 962.00) ^b	216.20 (172.10, 296.20) ^b	277.80 (141.00, 362.30) ^b	169.15 (106.60, 259.10) ^b
min/max	500.1/1351.3	123.3/438.8	71.8/668.2	64.0/748.5

	Subject Group - Angiotensinogen (nmol/L)			
Time Point	Pooled Placebo	ION904 30 mg	ION904 60 mg	ION904 90 mg
Day 85	(n=10)	(n=9)	(n=9)	(n=8)
Mean	714.77	281.84	307.94	260.00
	(230.709, 72.957) ^a	(124.432, 41.477) ^a	(146.360, 48.787) ^a	(226.431, 80.056) ^a
Median	699.05	292.70	312.40	217.25
	(620.40, 825.10)	(172.50, 354.20)	(192.50, 370.50)	(132.80, 230.70)
min/max	331.4/1169.8	118.4/451.8	88.2/552.3	112.1/806.4
Day 99	(n=10)	(n=9)	(n=9)	(n=8)
Mean	815.64	213.07	260.23	191.70
	(201.805, 63.816) ^a	(81.710, 27.237) ^a	(203.000, 67.667) ^a	(224.061, 79.218) ^a
Median	808.80	208.90	205.40	110.10
	(650.90, 857.50) ^b	(168.70, 293.90) ^b	(127.30, 321.00) ^b	(89.10, 174.80) ^b
min/max	602.7/1289.4	97.8/326.7	57.9/733.1	49.9/735.7
Day 113	(n=10)	(n=10)	(n=11)	(n=12)
Mean	768.90	305.58	348.47	298.08
	(167.519, 52.974) ^a	(130.405, 41.238) ^a	(207.823, 62.661) ^a	(203.004, 58.602) ^a
Median	746.75	294.60	358.40	245.25
	(731.40, 818.80) ^b	(235.00, 429.20) ^b	(151.80, 472.40) ^b	(172.05, 421.20) ^b
min/max	532.8/1149.3	85.9/511.1	90.6/780.7	57.4/716.5
Day 127	(n=10)	(n=10)	(n=11)	(n=12)
Mean	745.04	298.57	416.72	344.68
	(156.523, 49.497) ^a	(132.307, 41.839) ^a	(221.629, 66.824) ^a	(207.290, 59.839) ^a
Median	777.10	319.45	416.80	252.65
	(595.20, 865.70) ^b	(153.20, 397.70) ^b	(256.10, 524.70)	(219.80, 477.35)
min/max	514.8/966.4	130.9/513.4	134.3/899.2	125.0/805.3
Day 155	(n=10)	(n=10)	(n=12)	(n=12)
Mean	807.51	457.47	507.73	463.49
	(159.937, 50.576) ^a	(242.508, 76.688) ^a	(194.806, 56.236) ^a	(208.782, 60.270) ^a
Median	761.15	390.50	541.70	434.30
	(751.70, 836.50) ^b	(342.40, 568.80) ^b	(330.70, 604.15) ^b	(325.60, 556.90) ^b
min/max	608.5/1198.2	188.4/1039.6	232.1/823.8	158.8/829.4
Day 176	(n=10)	(n=10)	(n=11)	(n=12)
Mean	813.11	477.89	589.02	467.78
	(172.768, 54.634) ^a	(247.822, 78.368) ^a	(210.647, 63.512) ^a	(168.284, 48.580) ^a
Median	832.65	434.80	685.30	512.05
	(634.00, 950.40) ^b	(336.20, 500.40) ^b	(375.10, 761.70) ^b	(334.95, 585.70) ^b
min/max	583.0/1086.5	204.0/1056.9	327.8/921.4	188.8/699.7

^a(SD, SEM), ^b(P25, P75)

[0668] Table 21: Percent change in plasma AGT protein levels from baseline over time.

Time Point	Subject Group - Percent Change in Plasma AGT Protein from Baseline			
	Pooled Placebo	ION904 30 mg	ION904 60 mg	ION904 90 mg
Day 15				
Mean	(n=12) -10.1 (13.2, 3.8) ^a	(n=10) -49.8 (19.8, 6.3) ^a	(n=13) -58.4 (22.7, 6.3) ^a	(n=12) -71.5 (17.7, 5.1) ^a
Median	-10.6 (-20.8, -0.6) ^b	-47.6 (-66.4, -35.1) ^b	-70.0 (-75.3, -42.2) ^b	-73.7 (-85.8, -65.0) ^b
min/max	-30.0/15.2	-80.7/-13.7	-80.6/-12.1	-88.4, -31.7
P-value ^c		<0.001	<0.001	<0.001
Day 29				
Mean	(n=12) -9.9 (15.6, 4.5) ^a	(n=10) -47.6 (14.3, 4.5) ^a	(n=13) -60.2 (18.5, 5.1) ^a	(n=12) -68.9 (16.4, 4.7) ^a
Median	-11.7 (-19.9, 2.7) ^b	-48.1 (-62.8, -32.9) ^b	-65.7 (-74.4, -56.2) ^b	-70.7 (-80.7, -63.7) ^b
min/max	-37.5/13.2	-67.4,-31.0	-79.7/-27.1	-84.8, -25.3
P-value ^c		<0.001	<0.001	<0.001
Day 43				
Mean	(n=11) -3.1 (16.6, 5.0) ^a	(n=10) -58.0 (21.6, 6.8) ^a	(n=13) -68.9 (20.2, 5.6) ^a	(n=12) -76.1 (19.8, 5.7) ^a
Median	-3.8 (-21.4, 14.2) ^b	-59.4 (-76.9, -40.1) ^b	-74.4 (-82.0, -57.2) ^b	-83.1 (-88.7, -72.1) ^b
min/max	-24.2/23.8	-84.7/-23.7	-90.0/-21.5	-90.5/-21.0
P-value ^c		<0.001	<0.001	<0.001
Day 57				
Mean	(n=11) -5.7 (22.0, 6.6) ^a	(n=9) -56.9 (18.1, 6.0) ^a	(n=11) -60.1 (21.2, 6.4) ^a	(n=11) -72.8 (22.2, 6.7) ^a
Median	1.4 (-29.5, 10.2) ^b	-49.1 (-72.5, -44.2) ^b	-72.1 (-75.8, -38.0) ^b	-77.4 (-88.2, -69.3) ^b
min/max	-40.9/27.8	-79.2/-32.3	-83.4/-28.1	-89.9/-11.9
P-value ^c		<0.001	<0.001	<0.001
Day 71				
Mean	(n=11) -10.4 (19.8, 6.0) ^a	(n=9) -66.0 (14.8, 4.9) ^a	(n=11) -65.6 (21.3, 6.4) ^a	(n=10) -75.6 (22.0, 6.9) ^a
Median	-8.7 (-27.0, 5.6) ^b	-66.6 (-75.0, -56.3) ^b	-62.8 (-85.0, -50.8) ^b	-80.4 (-90.6, -73.6) ^b
min/max	-44.6/20.6	-85.6/-43.1	-91.5/-29.1	-93.1/-17.3
P-value ^c		<0.001	<0.001	<0.001

Subject Group - Percent Change in Plasma AGT Protein from Baseline				
Time Point	Pooled Placebo	ION904 30 mg	ION904 60 mg	ION904 90 mg
Day 85	(n=10)	(n=9)	(n=9)	(n=8)
Mean	-18.1	-62.5	-63.7	-70.9
	(19.9, 6.3) ^a	(14.2, 4.7) ^a	(19.0, 6.3) ^a	(25.2, 8.9) ^a
Median	-16.7	-63.7	-69.9	-76.5
	(-23.9, -4.7) ^b	(-74.1, -48.5) ^b	(-78.8, -44.3) ^b	(-85.0, -71.6) ^b
min/max	-65.2/4.4	-82.0/-41.5	-89.5/-38.3	-90.5/-10.9
P-value ^c		<0.001	<0.001	<0.001
Day 99	(n=10)	(n=9)	(n=9)	(n=8)
Mean	-6.4	-70.7	-69.9	-79.0
	(15.1, 4.8) ^a	(11.6, 3.9) ^a	(22.6, 7.5) ^a	(24.7, 8.7) ^a
Median	-4.6	-73.8	-78.5	-85.7
	(-22.8, 4.8) ^b	(-75.5, -61.9) ^b	(-85.0, -58.7) ^b	(-92.0, -82.1) ^b
min/max	-25.1/15.1	-88.6/-51.2	-93.1/-22.3	-93.4/-18.8
P-value ^d		<0.001	<0.001	0.001
Day 113	(n=10)	(n=10)	(n=11)	(n=12)
Mean	-11.2	-58.8	-63.3	-67.5
	(15.4, 4.9) ^a	(16.3, 5.2) ^a	(22.5, 6.8) ^a	(22.9, 6.6) ^a
Median	-8.9	-51.9	-69.6	-75.6
	(-21.2, 2.4) ^b	(-66.6, -46.1) ^b	(-82.1, -48.3) ^b	(-82.0, -50.6) ^b
min/max	-35.7/10.1	-89.9/-43.7	-89.2/-17.2	-92.7/-20.9
P-value ^c		<0.001	<0.001	<0.001
Day 127	(n=10)	(n=10)	(n=11)	(n=12)
Mean	-14.2	-61.6	-56.5	-61.9
	(13.7, 4.3) ^a	(13.2, 4.2) ^a	(22.8, 6.9) ^a	(23.5, 6.8) ^a
Median	-11.4	-60.9	-63.9	-70.0
	(-22.5, -2.1) ^b	(-71.4, -53.0) ^b	(-72.8, -43.9) ^b	(-80.6, -44.9) ^b
min/max	-42.5/0.5	-84.5/-43.5	-84.1/-4.6	-89.0/-11.1
P-value ^c		<0.001	<0.001	<0.001
Day 155	(n=10)	(n=10)	(n=12)	(n=12)
Mean	-6.3	-43.4	-46.8	-49.9
	(17.0, 5.4) ^a	(15.5, 4.9) ^a	(20.2, 5.8) ^a	(22.8, 6.6) ^a
Median	-11.1	-48.6	-49.2	-54.0
	(-19.8, 6.9) ^b	(-56.5, -31.6) ^b	(-63.4, -27.3) ^b	(-62.4, -41.3) ^b
min/max	-25.8/24.4	-58.8/-11.2	-72.4/-17.7	-80.4/-8.4
P-value ^c		<0.001	<0.001	<0.001
Day 176	(n=10)	(n=10)	(n=11)	(n=12)
Mean	-5.2	-40.4	-35.6	-48.8
	(22.0, 7.0) ^a	(17.2, 5.4) ^a	(22.9, 6.9) ^a	(19.4, 5.6) ^a
Median	-7.7	-42.4	-36.6	-49.4
	(-23.2, 15.5) ^b	(-55.4, -25.4) ^b	(-57.7, -21.7) ^b	(-64.4, -30.9) ^b
min/max	-33.2/33.7	-64.8/-9.7	-61.1/4.4	-79.8/-22.7
P-value ^c		<0.001	0.002	<0.001

^a(SD, SEM), ^b(P25, P75), ^cthe stratification factor (current use of ACEi/ARB vs. no current use of ACEi/ARB), treatment, and baseline measure are included in the Analysis of Covariate (ANCOVA) model as independent variables, ^dthe stratification factor (current use of ACEi/ARB vs. no current use of ACEi/ARB) and treatment are included in the Van Elteren Test.

[0669] For the per protocol set, the results at Baseline and Study Day 99 are summarized in Table 22. For the primary endpoint, the mean percent change in plasma angiotensinogen from Baseline to Study Day 99/Week 15 was a reduction of -71%, -70%, and -79% for ION904 at 30 mg, 60 mg, and 90 mg, respectively, compared to -6% for placebo ($p \leq 0.001$ for all ION904 doses). The corresponding median percent change was 74% ($p < 0.001$) for ION904 at 30 mg, 79% ($p < 0.001$) for ION904 at 60 mg, and 86% ($p = 0.001$) for ION904 at 90 mg, compared to -5% for placebo. The majority of patients (75%) who received ION904 90 mg had a reduction in plasma angiotensinogen of $>80\%$ at Study Day 99.

[0670] Table 22: Per Protocol Set absolute levels, change, and percent change from Baseline to Day 99 in plasma AGT protein levels.

Per Protocol Set (N=39)				
Parameter	Pooled Placebo (N=11)	ION904 30 mg (N=9)	ION904 60 mg (N=10)	ION904 90 mg (N=9)
Baseline				
Mean (SD, SEM)	858 (168, 50.7)	764 (231, 76.9)	891 (231, 73.1)	911 (177, 58.8)
Median (P25, P75)	866 (687, 952)	772 (669, 864)	845 (743, 942)	906 (789, 993)
Day 99				
Mean (SD, SEM)	816 (202, 63.8)	213 (81.7, 27.2)	260 (203, 67.7)	192 (224, 79.2)
Median (P25, P75)	800 (651, 858)	209 (169, 294)	205 (127, 321)	110 (89.1, 175)
Day 99 Change from Baseline				
Mean (SD, SEM)	-59.9 (146, 46.3)	-551 (219, 73.1)	-631 (293, 97.6)	-734 (290, 102)
Median (P25, P75)	-39.1 (-217, 37)	-478 (-757, -343)	-667 (-784, -436)	-726 (-939, -638)
Normality test P-value (Shapiro-Wilk) ^[I]		<0.001	<0.001	<0.001
P-value		<0.001 ^[IV]	<0.001 ^[IV]	0.001 ^[IV]
Day 99 Percent Change from Baseline				
Mean (SD, SEM)	-6.4 (15.1, 4.8)	-70.7 (11.6, 3.9)	-69.9 (22.6, 7.5)	-79.0 (24.7, 8.7)

Per Protocol Set (N=39)				
Parameter	Pooled Placebo (N=11)	ION904 30 mg (N=9)	ION904 60 mg (N=10)	ION904 90 mg (N=9)
Median (P25, P75)	-4.6 (-22.8, 4.8)	-73.8 (-75.5, -61.9)	-78.5 (-85.0, -58.7)	-85.7 (-92.0, -82.1)
Normality test P-value (Shapiro-Wilk) ^[I]		0.004	0.004	0.004
P-value		<0.001 ^[V]	<0.001 ^[V]	0.001 ^[V]

Note: The baseline for plasma angiotensinogen was defined as the average of all values prior to the first dose of Study Drug.

^[I]The normality assumption was assessed by the Shapiro-Wilk test based on the residuals from ANCOVA. If Normality P-value was significant (P-value ≤ 0.01), Van Elteren test was used.

^[A]The stratification factor (current use of ACE/ARB vs. no current use of ACE/ARB), treatment, and baseline measure was included in the Analysis of Covariate (ANCOVA) model as an independent variable.

^[V]The stratification factor (current use of ACE/ARB vs. no current use of ACE/ARB) and treatment was included in the Van Elteren Test.

[0671] Change and percent change from Baseline in mean plasma angiotensinogen showed a statistically significant reduction with all doses of ION904 ($p \leq 0.003$ vs. placebo) at every post-Baseline visit, from Day 15 through Day 176, in both the per protocol set (PPS) and the full analysis set. Statistically significant percent changes in mean plasma angiotensinogen were noted ranging from -36% to -79% compared to placebo angiotensinogen reductions with a range of -18% to -3%. The median percent change in plasma angiotensinogen was greater in ION904-treated patients compared to placebo (-43% to -86% vs. 1% to -17%, respectively). The mean and median angiotensinogen reductions were sustained throughout the post-treatment period.

[0672] A waterfall plot of individual responses in the ION904-treated groups and placebo groups is shown in FIG. 7. The placebo had modest changes, whereas the effect of ION904 had a relatively dose dependent relationship to angiotensinogen knockdown.

[0673] Secondary Endpoints: Seated-Automated Office SBP and DBP

[0674] A larger proportion of subjects (11/26, 42%) in the ION904 group achieved ≥ 10 mmHg reductions in SBP compared to PBO (3/10, 30%) at week 15. However, only the 60 mg ION904 treatment group compared to placebo demonstrated a statistically significant mean reduction in

systolic blood pressure (-10 mmHg, PBO subtracted; $p=0.04$; see Tables 23-25, and FIG. 8; all values from analysis of per protocol population $n=39$). The effect of ION904 on systolic blood pressure was an exploratory endpoint because, in general, the number of subjects in the treatment groups was less than the number required in order to definitively identify a statistically significant change in blood pressure. A confirmed systolic blood pressure less than 90 mmHg was not observed. DBP data are set forth in Table 26 and shown in FIG. 9. Results for the full analysis set were similar to those for the per protocol set.

[0675] Table 23: Seated automated SBP in subjects with uncontrolled blood pressure.

Subject Group - Seated Automated Systolic Blood Pressure (mmHg)				
Time Point	Pooled Placebo	ION904 30 mg	ION904 60 mg	ION904 90 mg
Baseline	(n=11)	(n=9)	(n=10)	(n=9)
Mean	146.1 (8.36, 2.52) ^a	141.4 (10.82, 3.61) ^a	146.1 (11.95, 3.78) ^a	144.6 (13.29, 4.43) ^a
Median	144.0 (140.0, 150.0) ^b	136.0 (134.0, 144.0) ^b	148.5 (133.0, 153.0) ^b	141.0 (134.0, 155.0) ^b
min/max	133/162	131/163	131/164	130/168
Day 15	(n=11)	(n=8)	(n=10)	(n=9)
Mean	135.5 (13.27, 4.00) ^a	134.4 (15.93, 5.63) ^a	140.1 (20.29, 6.42) ^a	137.9 (18.39, 6.13) ^a
Median	137.0 (123.0, 145.0) ^b	136.0 (121.5, 147.5) ^b	135.5 (131.0, 150.0) ^b	138.0 (134.0, 142.0) ^b
min/max	114/155	111/154	107/184	100/169
Day 29	(n=11)	(n=9)	(n=10)	(n=9)
Mean	139.5 (10.14, 3.06) ^a	133.9 (13.59, 4.53) ^a	131.7 (15.42, 4.88) ^a	135.0 (18.43, 6.14) ^a
Median	140.0 (132.0, 146.0) ^b	127.0 (126.0, 140.0) ^b	130.0 (121.0, 140.0) ^b	143.0 (115.0, 145.0) ^b
min/max	124/159	118/160	110/165	114/163
Day 43	(n=11)	(n=9)	(n=10)	(n=9)
Mean	141.1 (14.13, 4.26) ^a	131.4 (9.71, 3.24) ^a	127.1 (14.10, 4.46) ^a	133.9 (15.40, 5.13) ^a
Median	138.0 (129.0, 153.0) ^b	128.0 (124.0, 142.0) ^b	121.5 (118.0, 139.0) ^b	126.0 (124.0, 141.0) ^b
min/max	119/161	120/146	113/157	114/161
Day 57	(n=11)	(n=9)	(n=10)	(n=9)
Mean	136.8 (10.17, 3.07) ^a	132.3 (14.40, 4.80) ^a	128.9 (13.52, 4.28) ^a	134.3 (13.44, 4.48) ^a
Median	135.0 (128.0, 148.0) ^b	130.0 (125.0, 140.0) ^b	129.0 (119.0, 136.0) ^b	133.0 (126.0, 146.0) ^b
min/max	123/155	113/162	111/158	115/153

	Subject Group - Seated Automated Systolic Blood Pressure (mmHg)			
Time Point	Pooled Placebo	ION904 30 mg	ION904 60 mg	ION904 90 mg
Day 71	(n=11)	(n=9)	(n=10)	(n=9)
Mean	137.6	129.8	136.6	134.3
	(14.12, 4.26) ^a	(12.04, 4.01) ^a	(14.68, 4.64) ^a	(9.67, 3.22) ^a
Median	139.0	132.0	137.0	136.0
	(134.0, 148.0) ^b	(119.0, 135.0) ^b	(123.0, 145.0) ^b	(128.0, 140.0) ^b
min/max	110/156	113/148	118/164	121/147
Day 85	(n=10)	(n=9)	(n=9)	(n=8)
Mean	141.0	136.1	127.7	139.6
	(15.94, 5.04) ^a	(18.88, 6.29) ^a	(13.05, 4.35) ^a	(13.28, 4.69) ^a
Median	140.0	138.0	123.0	137.0
	(129.0, 149.0) ^b	(123.0, 154.0) ^b	(119.0, 133.0) ^b	(129.0, 148.5) ^b
min/max	121/176	104/160	112/151	127/161
Day 99	(n=10)	(n=9)	(n=9)	(n=8)
Mean	143.8	134.2	132.1	142.4
	(11.46, 3.62) ^a	(10.67, 3.56) ^a	(9.65, 3.22) ^a	(12.24, 4.33) ^a
Median	143.5	133.0	131.0	138.0
	(137.0, 151.0) ^b	(130.0, 139.0) ^b	(125.0, 140.0) ^b	(133.0, 153.5) ^b
min/max	125/166	116/154	117/144	129/161
Day 113	(n=10)	(n=9)	(n=9)	(n=9)
Mean	139.0	129.8	134.1	136.2
	(16.60, 5.25) ^a	(11.30, 3.77) ^a	(8.68, 2.89) ^a	(21.08, 7.03) ^a
Median	139.0	132.0	135.0	136.0
	(125.0, 143.0) ^b	(125.0, 138.0) ^b	(130.0, 139.0) ^b	(125.0, 145.0) ^b
min/max	114/174	104/140	118/148	107/172
Day 127	(n=10)	(n=9)	(n=9)	(n=9)
Mean	142.6	132.3	134.8	135.9
	(20.12, 6.36) ^a	(8.50, 2.83) ^a	(13.34, 4.45) ^a	(15.00, 5.00) ^a
Median	136.5	131.0	136.0	135.0
	(130.0, 163.0) ^b	(127.0, 139.0) ^b	(122.0, 147.0) ^b	(131.0, 140.0) ^b
min/max	115/171	120/147	114/150	108/161
Day 155	(n=10)	(n=9)	(n=9)	(n=9)
Mean	145.7	129.9	133.6	137.1
	(16.43, 5.19) ^a	(10.28, 3.43) ^a	(12.19, 4.06) ^a	(23.77, 7.92) ^a
Median	146.0	128.0	134.0	133.0
	(134.0, 156.0) ^b	(124.0, 131.0) ^b	(125.0, 144.0) ^b	(127.0, 154.0) ^b
min/max	114/171	119/153	117/149	88/164
Day 176	(n=10)	(n=9)	(n=8)	(n=9)
Mean	151.2	131.8	140.1	131.8
	(17.15, 5.42) ^a	(9.42, 3.14) ^a	(13.30, 4.70) ^a	(10.97, 3.66) ^a
Median	151.0	129.0	137.0	129.0
	(141.0, 161.0) ^b	(124.0, 141.0) ^b	(129.0, 151.5) ^b	(126.0, 134.0) ^b
min/max	120/185	119/144	125/161	116/153

^a(SD, SEM), ^b(P25, P75), ^cthe stratification factor (current use of ACEi/ARB vs. no current use of ACEi/ARB), treatment, and baseline measure are included in the Analysis of Covariate (ANCOVA) model as independent variables

[0676] Table 24: Change in seated automated systolic blood pressure (ANCOVA) from baseline over time.

Subject Group - Change in Seated Automated Systolic Blood Pressure from Baseline				
Time Point	Pooled Placebo	ION904 30 mg	ION904 60 mg	ION904 90 mg
Day 15	(n=11)	(n=8)	(n=10)	(n=9)
Mean	-10.5 (9.30, 2.80) ^a	-7.8 (10.95, 3.87) ^a	-6.0 (18.97, 6.00) ^a	-6.7 (13.53, 4.51) ^a
Median	-14.0 (-17.0, -3.0) ^b	-10.0 (-16.0, 0.0) ^b	-6.0 (-14.0, -1.0) ^b	-5.0 (-13.0, 1.0) ^b
min/max	-25/2	-20/10	-41/35	-30/11
P-value ^c		0.794	0.539	0.578
Day 29	(n=11)	(n=9)	(n=10)	(n=9)
Mean	-6.6 (8.49, 2.56) ^a	-7.6 (10.97, 3.66) ^a	-14.4 (14.98, 4.74) ^a	-9.6 (19.16, 6.39) ^a
Median	-6.0 (-16.0, 1.0) ^b	-10.0 (-13.0, -5.0) ^b	-20.0 (-21.0, -2.0) ^b	-12.0 (-18.0, 9.0) ^b
min/max	-18/9	-23/13	-32/12	-43/16
P-value ^c		0.675	0.209	0.565
Day 43	(n=11)	(n=9)	(n=10)	(n=9)
Mean	-5.0 (12.66, 3.82) ^a	-10.0 (11.93, 3.98) ^a	-19.0 (8.52, 2.70) ^a	-10.7 (14.15, 4.72) ^a
Median	-4.0 (-16.0, 6.0) ^b	-12.0 (-20.0, -3.0) ^b	-17.5 (-25.0, -14.0) ^b	-10.0 (-18.0, -6.0) ^b
min/max	-24/17	-22/10	-34/-7	-32/20
P-value ^c		0.258	0.012	0.255
Day 57	(n=11)	(n=9)	(n=10)	(n=9)
Mean	-9.3 (13.00, 3.92) ^a	-9.1 (13.30, 4.43) ^a	-17.2 (13.05, 4.13) ^a	-10.2 (18.19, 6.06) ^a
Median	-10.0 (-22.0, 5.0) ^b	-11.0 (-14.0, -10.0) ^b	-18.5 (-24.0, -7.0) ^b	-12.0 (-22.0, 3.0) ^b
min/max	-27/11	-23/22	-37/5	-35/14
P-value ^c		0.532	0.135	0.706

	Subject Group - Change in Seated Automated Systolic Blood Pressure from Baseline			
Time Point	Pooled Placebo	ION904 30 mg	ION904 60 mg	ION904 90 mg
Day 71				
Mean	(n=11) -8.5 (11.56, 3.49) ^a	(n=9) -11.7 (8.53, 2.84) ^a	(n=10) -9.5 (13.50, 4.27) ^a	(n=9) -10.2 (14.26, 4.75) ^a
Median	-6.0 (-15.0, -1.0) ^b	-10.0 (-19.0, -7.0) ^b	-10.0 (-20.0, 0.0) ^b	-8.0 (-11.0, -3.0) ^b
min/max	-27/13	-23/1	-30/14	-37/6
P-value ^c		0.301	0.789	0.631
Day 85				
Mean	(n=10) -4.7 (13.78, 4.36) ^a	(n=9) -5.3 (15.48, 5.16) ^a	(n=9) -16.4 (12.28, 4.09) ^a	(n=8) -6.8 (18.42, 6.51) ^a
Median	-4.5 (-17.0, 6.0) ^b	1.0 (-11.0, 2.0) ^b	-13.0 (-27.0, -10.0) ^b	-4.0 (-24.0, 7.5) ^b
min/max	-22/18	-30/18	-36/2	-31/18
P-value ^c		0.766	0.084	0.777
Day 99				
Mean	(n=10) -1.9 (14.31, 4.53) ^a	(n=9) -7.2 (11.62, 3.87) ^a	(n=9) -12.0 (10.14, 3.38) ^a	(n=8) -4.0 (19.68, 6.96) ^a
Median	2.0 (-15.0, 5.0) ^b	-9.0 (-15.0, -3.0) ^b	-13.0 (-15.0, -7.0) ^b	3.0 (-17.5, 9.0) ^b
min/max	-25/22	-24/14	-29/6	-38, 17
P-value ^c		0.122	0.040	0.710
Day 113				
Mean	(n=10) -6.7 (19.03, 6.02) ^a	(n=9) -11.7 (12.13, 4.04) ^a	(n=9) -10.0 (8.59, 2.86) ^a	(n=9) -8.3 (16.77, 5.59) ^a
Median	-11.0 (-21.0, 9.0) ^b	-10.0 (-19.0, -2.0) ^b	-13.0 (-15.0, -5.0) ^b	-10.0 (-20.0, 4.0) ^b
min/max	-29/30	-30/4	-21/6	-33/16
P-value ^c		0.346	0.585	0.739
Day 127				
Mean	(n=10) -3.1 (18.96, 6.00) ^a	(n=9) -9.1 (11.74, 3.91) ^a	(n=9) -9.3 (9.27, 3.09) ^a	(n=9) -8.7 (13.98, 4.66) ^a
Median	-6.5 (-18.0, 13.0) ^b	-11.0 (-17.0, 3.0) ^b	-9.0 (-12.0, -6.0) ^b	-4.0 (-17.0, -1.0) ^b
min/max	-30/23	-24/7	-26/5	-32/14
P-value ^c		0.287	0.326	0.335
Day 155				
Mean	(n=10) 0.0 (13.80, 4.36) ^a	(n=9) -11.6 (11.75, 3.92) ^a	(n=9) -10.6 (9.18, 3.06) ^a	(n=9) -7.4 (22.38, 7.46) ^a
Median	2.0 (-15.0, 12.0) ^b	-5.0 (-16.0, -3.0) ^b	-9.0 (-14.0, -6.0) ^b	-9.0 (-22.0, 15.0) ^b
min/max	-19/20	-35/-2	-28/1	-42/23
P-value ^c		0.084	0.130	0.268

	Subject Group - Change in Seated Automated Systolic Blood Pressure from Baseline			
Time Point	Pooled Placebo	ION904 30 mg	ION904 60 mg	ION904 90 mg
Day 176	(n=10)	(n=9)	(n=8)	(n=9)
Mean	5.5 (18.27, 5.78) ^a	-9.7 (14.80, 4.93) ^a	-4.8 (9.72, 3.44) ^a	-12.8 (14.70, 4.90) ^a
Median	4.5 (-9.0, 19.0) ^b	-12.0 (-15.0, 4.0) ^b	-5.0 (-10.5, 0.5) ^b	-15.0 (-20.0, -3.0) ^b
min/max	-20/41	-39/10	-20/12	-32/14
P-value ^c		0.006	0.092	0.004

^a(SD, SEM), ^b(P25, P75), ^cthe stratification factor (current use of ACEi/ARB vs. no current use of ACEi/ARB), treatment, and baseline measure are included in the Analysis of Covariate (ANCOVA) model as independent variables

[0677] Table 25: Mean (± SEM) change from Baseline in seated automated office SBP over time (Per-Protocol Set).

Per Protocol Set (N=39)				
Systolic Blood Pressure	Pooled Placebo (N=11)	ION904 30 mg (N=9)	ION904 60 mg (N=10)	ION904 90 mg (N=9)
Baseline				
Mean (SD, SEM) ^a	146 (8.36, 2.52)	141 (10.8, 3.61)	146 (12, 3.78)	145 (13.29, 4.43)
Day 99				
Mean (SD, SEM)	144 (11.5, 3.62)	134 (10.7, 3.56)	132 (9.65, 3.22)	142 (12.2, 4.33)
Day 99 Change from Baseline				
Mean (SD, SEM)	-1.9 (14.3, 4.53)	-7.2 (11.6, 3.87)	-12.0 (10.1, 3.38)	-4.0 (19.7, 6.96)
LS Mean (95% CI)	0.1 (-7.2, 7.4)	-8.1 (-16.2, 0.0)	-10.8 (-18.7, -2.9)	-1.8 (-9.9, 6.2)
LS Mean of the difference (95% CI)		-8.2 (-18.7, 2.3)	-10.9 (-21.3, -0.5)	-2.0 (-12.7, 8.7)
Normality test P-value (Shapiro-Wilk) ^b		0.361	0.361	0.361
P-value		0.122 ^c	0.040 ^c	0.710 ^c

^a The baseline was defined as the last non-missing measurement prior to the first dose of Study Drug.

^b The normality assumption was assessed by the Shapiro-Wilk test based on the residuals from ANCOVA. If the normality p-value was significant (≤ 0.01), the Van Elteren test was used.

^c The stratification factor (current use of ACEi/ARB vs. no current use of ACEi/ARB), treatment, and baseline measure was included in the analysis of covariate (ANCOVA) model as an independent variable.

[0678] Table 26: Mean ($\pm$ SEM) change from Baseline in seated automated office DBP over time (Per-Protocol Set).

Per Protocol Set (N=39)				
Diastolic Blood Pressure	Pooled Placebo (N=11)	ION904 30 mg (N=9)	ION904 60 mg (N=10)	ION904 90 mg (N=9)
Baseline				
Mean (SD, SEM) ^a	85.6 (11.9, 3.59)	86.6 (12.8, 4.27)	84.6 (10.8, 3.42)	80.8 (12.7, 4.23)
Day 99				
Mean (SD, SEM)	81.9 (6.90, 2.18)	78.1 (8.46, 2.82)	77.9 (11.7, 3.89)	78.6 (10.6, 3.76)
Day 99 Change from Baseline				
Mean (SD, SEM)	-2.5 (8.59, 2.72)	-8.4 (10.4, 3.48)	-5.6 (5.27, 1.76)	-3.4 (13.4, 4.73)
Median (P25, P75)	0.5 (-5.0, 3.0)	-6.0 (-13.0, -4.0)	-4.0 (-10.0, -1.0)	-3.5 (-7.5, 1.5)
Min, Max	-23, 4	-31, 5	-15, 0	-28, 20
LS Mean (95% CI)	-2.2 (-7.3, 2.9)	-7.0 (-12.5, -1.5)	-5.6 (-11.2, -0.1)	-4.3 (-10.0, 1.3)
LS Mean of the difference (95% CI)		-4.8 (-12.0, 2.4)	-3.5 (-10.7, 3.8)	-2.2 (-9.6, 5.3)
Normality test P-value (Shapiro-Wilk) ^b		0.111	0.111	0.111
P-value		0.187 ^c	0.337 ^c	0.561 ^c

^a The baseline was defined as the last non-missing measurement prior to the first dose of Study Drug.

^b The normality assumption was assessed by the Shapiro-Wilk test based on the residuals from ANCOVA. If the normality p-value was significant (≤ 0.01), the Van Elteren test was used.

^c The stratification factor (current use of ACEi/ARB vs. no current use of ACEi/ARB), treatment, and baseline measure was included in the analysis of covariate (ANCOVA) model as an independent variable.

[0679] Pharmacokinetics and Immunogenicity

[0680] Plasma exposure was dose-dependent with concentrations appearing to reach steady-state by the end of the 12-week dosing period for the lower dose cohorts and approaching steady-state for the

highest dose cohort. The plasma elimination half-life of ION904 was approximately 3 to 4 weeks, reflecting the long tissue half-life of ION904. In addition, the overall incidence of treatment-emergent immunogenicity was relatively low (16.7%), as was the median peak titer of 300, while median onset was observed at 60 days. There did not appear to be any notable impact of ADA positivity on PK measures, however, the number of patients with positive ADA in each cohort was low, making a comparison difficult.

[0681] Safety and Tolerability

[0682] ION904 was generally well-tolerated. A summary of TEAEs is provided in Tables 27 and 28. The most frequently reported TEAEs for patients who received ION904 were injection site erythema (0% placebo, 19.4% ION904), headache (8.3% placebo, 11.1% ION904), and injection site pruritus (0% placebo, 8.3% ION904). Most TEAEs were reported as mild or moderate, and no dose dependency was noted for TEAEs. No flu-like reactions and no adverse events of special interest (AESIs) were reported. 6 TEAEs were reported as severe for 3 ION904-treated patients. No clinically meaningful platelet signal or thrombocytopenia was observed with ION904 treatment. No clinically meaningful liver signal (ALT/AST > 3X ULN) was observed with ION904 treatment. No renal signal related to ION904 treatment was observed. No AEs were reported for hyperkalemia. No deaths occurred during the study. In summary, clinically meaningful decreases in eGFR, increases in serum potassium, signals for hyperkalemia, renal dysfunction, hypotension, liver dysfunction, or thrombocytopenia were not observed; and no drug-related serious adverse events occurred.

[0683] Table 27: Treatment-emergent adverse events reported for at least 5% of placebo-treated, 30 mg ION904-treated, and 60 mg ION904-treated patients.

System Organ Class	Placebo (N=12)		ION904 30 mg (N=11)		ION904 60 mg (N=13)	
	Patients (%)	Events	Patients (%)	Events	Patients (%)	Events
General disorders and administration site conditions						
Injection site erythema	0	0	3 (27.3)	9	2 (15.4)	3
Injection site pruritus	0	0	0	0	2 (15.4)	2
Infections and infestations						
COVID-19	0	0	1 (9.1)	1	0	0

System Organ Class	Placebo (N=12)		ION904 30 mg (N=11)		ION904 60 mg (N=13)	
	Patients (%)	Events	Patients (%)	Events	Patients (%)	Events
Upper respiratory tract infection	0	0	0	0	2 (15.4)	2
Urinary tract infection	1 (8.3)	1	1 (9.1)	2	0	0
Respiratory, thoracic and mediastinal disorders						
Dyspnea	0	0	0	0	2 (15.4)	2
Musculoskeletal and connective tissue disorders						
Back pain	0	0	0	0	2 (15.4)	2
Nervous system disorders						
Headache	1 (8.3)	1	0	0	0	0
Vascular disorders						
Hypotension	0	0	0	0	1 (7.7)	1

[0684] Table 28: Treatment-emergent adverse events reported for at least 5% of 90 mg ION904-treated and all ION904-treated patients.

System Organ Class	ION904 90 mg (N=12)		ION904 Total (N=36)	
	Patients (%)	Events	Patients (%)	Events
General disorders and administration site conditions				
Injection site erythema	2 (16.7)	5	7 (19.4)	17
Injection site pruritus	1 (8.3)	1	3 (8.3)	3
Infections and infestations				
COVID-19	1 (8.3)	1	2 (5.6)	2
Upper respiratory tract infection	0	0	2 (5.6)	2

System Organ Class	ION904 90 mg (N=12)		ION904 Total (N=36)	
	Patients (%)	Events	Patients (%)	Events
Urinary tract infection	1 (8.3)	1	2 (5.8)	3
Respiratory, thoracic and mediastinal disorders				
Dyspnea	0	0	2 (5.6)	2
Musculoskeletal and connective tissue disorders				
Back pain	0	0	2 (5.6)	2
Nervous system disorders				
Headache	4 (33.3)	4	4 (11.1)	4
Vascular disorders				
Hypotension	1 (8.3)	1	2 (5.6)	2

[0685] Results of ION904 administration demonstrated significant reductions in plasma AGT protein levels, with a favorable safety and tolerability profile, though no significant impact on blood pressure in subjects with uncontrolled hypertension on one or more antihypertensive medications, however the study was not powered to detect changes in blood pressure. Notably, ION904 reductions were more potent and more durable as compared to ISIS 757456. Further, fewer, lower doses of ION904 achieved greater reductions in plasma AGT protein (e.g., 4 doses of 90 mg of ION904 over 15 weeks achieved a maximum median percent reduction of 86% in plasma AGT compared to baseline; whereas a maximum reduction of 63% in plasma AGT protein was achieved by day 57 after 8 doses of 120 mg of compound ISIS 757456, and a maximum reduction of 49% in plasma AGT protein was achieved by day 85 after 12 doses of 80 mg of compound ISIS 757456 (see Example 1), and up to a maximum reduction of 67% in AGT protein was seen in earlier studies).

[0686] Example 4: Study to Assess the Effect of ION904 in Patients with Heart Failure

[0687] Based on results from phase 1 and phase 2 studies, a multicenter, double-blind, randomized, placebo-controlled, dose-ranging study is designed to assess the effect of ION904 administration in subjects with heart failure and will include a subset of patients with moderate to severe renal dysfunction. Safety and efficacy of ION904 in treating heart failure with reduced ejection fraction

(HFrEF, i.e., EF <40%) will be evaluated in subjects having an NYHA functional class II-III classification, half of which will have an eGFR ≤ 45 ml/min/1.73 m² and half of which will have an eGFR >45 ml/min/1.73 m². The primary endpoint will be end systolic cardiac volume indexed to body surface area (ESVi) and/or end diastolic cardiac volume indexed to body surface area (EDVi) measured by echocardiogram; and secondary/exploratory end points will include percent change in plasma AGT protein level from baseline over time, cardiac function (EF, global longitudinal LV strain), serum biomarkers associated with remodeling (NT-proBNP and hs-Troponin), cardiac functional status (NYHA functional class), and patient-reported outcomes (KCCQ).

[0688] Subjects will be required to be on a stable regimen of guideline-recommended beta blockers and SGLT-2 inhibitors (in countries where they are approved) and they should be on maximally tolerated doses of RAAS inhibitors (ACE/ARB/ARNi or MRA), unless they have prior documented contraindication to one of these compounds, for at least 4 weeks prior to screening evaluations. Investigators will continue the stable regimen throughout the duration of study with some variation, as a change in any life-saving heart failure medications after Day 1 may be allowed at discretion of the investigator if warranted by the subject's condition. Subjects will be stratified by eGFR with 50% of the population having an eGFR >45 ml/min/1.73 m² and 50% of the population having an eGFR ≤ 45 ml/min/1.73 m². Further stratification will include NYHA class (i.e., II or III). Baseline demographic and disease characteristics as well as subjects' NYHA class will be summarized for each treatment group.

[0689] Effects of monthly subcutaneous injection of ION904 for six (6) months in patients with heart failure with reduced ejection fraction (HFrEF) stratified by glomerular filtration rate is evaluated. 60 mg of ION904 or 90 mg of ION904 is administered every four weeks over a study treatment period of 36 weeks or 52 weeks, beginning with a first dose of ION904 (or placebo) on day 1, and additional doses administered monthly (e.g, every 28 days or 4 weeks) and will culminate with a final dose at week 24. At week 28, effect of ION904 is evaluated by echocardiography to assess cardiac dimensions indicative of the extent of remodeling.

[0690] Additional evaluations will also be carried out throughout in-clinic visits at weeks prior to first dose and up to and including weeks 32 and 36. Baseline plasma AGT protein is the average of all values prior to a first dose of ION904. Baseline eGFR is the average of the pre-dose result closest to day 1 and day 1 result. Baseline for all other assessments is the last measurement prior to a first dose of ION904. Additional analyses include: (1) absolute levels, change, and percent change in plasma

AGT protein from baseline to each scheduled, post-baseline visit, up to week 36, (2) absolute level, change, and percent change in N-terminal prohormone of B-type natriuretic peptide (NT-proBNP), from baseline to each scheduled, post-baseline visit, up to week 36, (3) absolute levels, change, and percent change in high-sensitive cardiac troponin T (hs-cTnT) from baseline to each scheduled, post-baseline visit, up to week 36, (4) cardiac dimension measurements via echocardiography; cardiac function (EF, strain) and dimensions (ESVi, EDVi) on echocardiography, and (5) absolute levels, change and percent change of angiotensin II, renin (PRA, direct renin) from baseline to each scheduled, post-baseline visit, up to week 36. In addition, subject reported results including change in subject reported outcomes, Kansas City Cardiomyopathy Questionnaire (KCCQ) and EQ-5D-5L; and proportion of subjects reported CV mortality, HF hospitalization and urgent visits for HF as clinical outcomes are summarized by treatment group.

CLAIMS:

1. A method for reducing AGT RNA and/or AGT protein in a subject intolerant, or at risk of being intolerant, to treatment with a renin-angiotensin-aldosterone system (RAAS) inhibitor, comprising administering an oligomeric compound or salt thereof to a subject having or at risk for heart failure; wherein the subject is intolerant, or is at risk of being intolerant, to treatment with a RAAS inhibitor; and wherein the amount of AGT protein in the subject is reduced by at least 70%, at least 75%, at least 80% or at least 85% but less than 95% in the subject;

wherein the oligomeric compound is a GalNAc-conjugated modified oligonucleotide, wherein the modified oligonucleotide is represented by the following chemical notation (5' to 3'):

${}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 4) or a salt thereof; wherein:

A = an adenine nucleobase,

${}^m\text{C}$ = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

k = a cEt sugar moiety,

d = an unmodified DNA sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage;

and wherein GalNAc is an N-acetyl galactosamine conjugate moiety.

2. A method of treating heart failure in a subject, comprising administering an oligomeric compound or a salt thereof to a subject having or at risk of having heart failure, wherein the subject is or is at risk of being intolerant to treatment with a RAAS inhibitor; wherein treatment results in amelioration of one or more symptoms and/or lack of progression of heart failure;

wherein the oligomeric compound is a GalNAc-conjugated modified oligonucleotide, wherein the modified oligonucleotide is represented by the following chemical notation (5' to 3'):

${}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 4) or a salt thereof; wherein:

A = an adenine nucleobase,

${}^m\text{C}$ = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

k = a cEt sugar moiety,

d = an unmodified DNA sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage;

and wherein GalNAc is an N-acetyl galactosamine conjugate moiety.

3. A method of treating heart failure in a subject, comprising administering about 50 mg to about 200 mg an oligomeric compound or a salt thereof to a subject; wherein administering oligomeric compound results in amelioration of one or more symptoms and/or lack of progression of heart failure; wherein the oligomeric compound is a GalNAc-conjugated modified oligonucleotide, wherein the modified oligonucleotide is represented by the following chemical notation (5' to 3'):

${}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 4) or a salt thereof; wherein:

A = an adenine nucleobase,
 ${}^m\text{C}$ = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 k = a cEt sugar moiety,
 d = an unmodified DNA sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage;

and wherein GalNAc is an N-acetyl galactosamine conjugate moiety.

4. Use of an oligomeric compound or a salt thereof for treating heart failure in a subject intolerant to, or at risk of being intolerant to, treatment with a RAAS inhibitor, wherein: heart failure in the subject does not progress or one or more symptoms are ameliorated; wherein the oligomeric compound is a GalNAc-conjugated modified oligonucleotide, wherein the modified oligonucleotide is represented by the following chemical notation (5' to 3'):

${}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 4) or a salt thereof; wherein:

A = an adenine nucleobase,
 ${}^m\text{C}$ = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 k = a cEt sugar moiety,
 d = an unmodified DNA sugar moiety,
 s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage;

and wherein GalNAc is an N-acetyl galactosamine conjugate moiety.

5. Use of 50 mg to 200 mg of an oligomeric compound or a salt thereof for treating heart failure in a subject having or at risk for heart failure;

wherein the oligomeric compound is a GalNAc-conjugated modified oligonucleotide, wherein the modified oligonucleotide is represented by the following chemical notation (5' to 3'):

${}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 4) or a salt thereof; wherein:

A = an adenine nucleobase,

${}^m\text{C}$ = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

k = a cEt sugar moiety,

d = an unmodified DNA sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage;

and wherein GalNAc is an N-acetyl galactosamine conjugate moiety.

6. Use of an oligomeric compound or a salt thereof for reducing AGT RNA and/or AGT protein in a subject intolerant, or at risk of being intolerant, to treatment with a renin-angiotensin-aldosterone system (RAAS) inhibitor;

wherein the oligomeric compound is a GalNAc conjugated modified oligonucleotide, wherein the modified oligonucleotide is represented by the following chemical notation (5' to 3'):

${}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 4) or a salt thereof; wherein:

A = an adenine nucleobase,

${}^m\text{C}$ = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

k = a cEt sugar moiety,

d = an unmodified DNA sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage;

wherein GalNAc= is an N-acetyl galactosamine conjugate moiety;

and wherein the oligomeric compound reduces AGT protein in a subject by at least 70%, at least 75%, at least

80% or at least 85% but less than 95%.

7. A method for administering an oligomeric compound to a subject, comprising administering 60 mg to 120 mg of an oligomeric compound or salt thereof to a subject having or at risk for heart failure with reduced ejection fraction (HFrEF); wherein the oligomeric compound is a GalNAc-conjugated modified oligonucleotide, wherein the modified oligonucleotide is represented by the following chemical notation (5' to 3'): ${}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 4) or a salt thereof; wherein:

A = an adenine nucleobase,

${}^m\text{C}$ = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

k = a cEt sugar moiety,

d = an unmodified DNA sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage;

and wherein GalNAc is an N-acetyl galactosamine conjugate moiety.

8. A method for reducing AGT RNA and/or AGT protein in a subject, comprising administering 60 mg to 120 mg of an oligomeric compound or salt thereof to a subject having or at risk for heart failure with reduced ejection fraction (HFrEF); wherein the oligomeric compound is a GalNAc-conjugated modified oligonucleotide, wherein the modified oligonucleotide is represented by the following chemical notation (5' to 3'): ${}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 4) or a salt thereof; wherein:

A = an adenine nucleobase,

${}^m\text{C}$ = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

k = a cEt sugar moiety,

d = an unmodified DNA sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage;

and wherein GalNAc is an N-acetyl galactosamine conjugate moiety.

9. Use of 60 mg to 120 mg of an oligomeric compound or a salt thereof for treating a subject having or at risk for heart failure with reduced ejection fraction (HFrEF); wherein the oligomeric compound is a GalNAc conjugated modified oligonucleotide, wherein the modified

oligonucleotide is represented by the following chemical notation (5' to 3'):

${}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 4) or a salt thereof; wherein:

A = an adenine nucleobase,

${}^m\text{C}$ = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

k = a cEt sugar moiety,

d = an unmodified DNA sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage;

wherein GalNAc= is an N-acetyl galactosamine conjugate moiety

10. Use of 60 mg to 120 mg of an oligomeric compound or a salt thereof for reducing AGT RNA and/or AGT protein in a subject having or at risk for heart failure with reduced ejection fraction (HFrEF); wherein the oligomeric compound is a GalNAc conjugated modified oligonucleotide, wherein the modified oligonucleotide is represented by the following chemical notation (5' to 3'):

${}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 4) or a salt thereof; wherein:

A = an adenine nucleobase,

${}^m\text{C}$ = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

k = a cEt sugar moiety,

d = an unmodified DNA sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage;

wherein GalNAc= is an N-acetyl galactosamine conjugate moiety.

11. The method or use of any one of claims 1-10, wherein the oligomeric compound is represented by the following chemical notation (5' to 3'):

THA-C6-GalNAc₃- ${}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 5) or a salt thereof; wherein,

A = an adenine nucleobase,

${}^m\text{C}$ = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

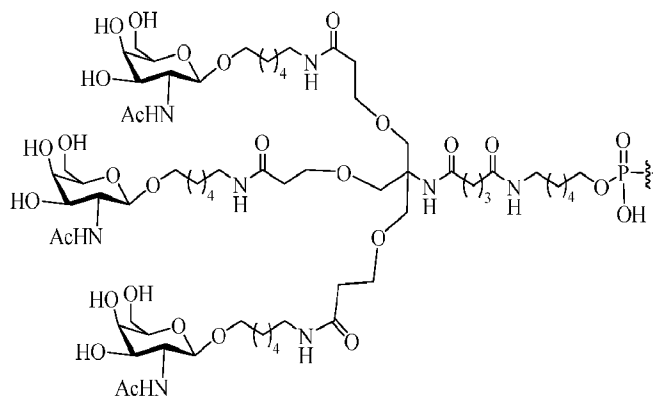
k = a cEt sugar moiety,

d = an unmodified DNA sugar moiety,

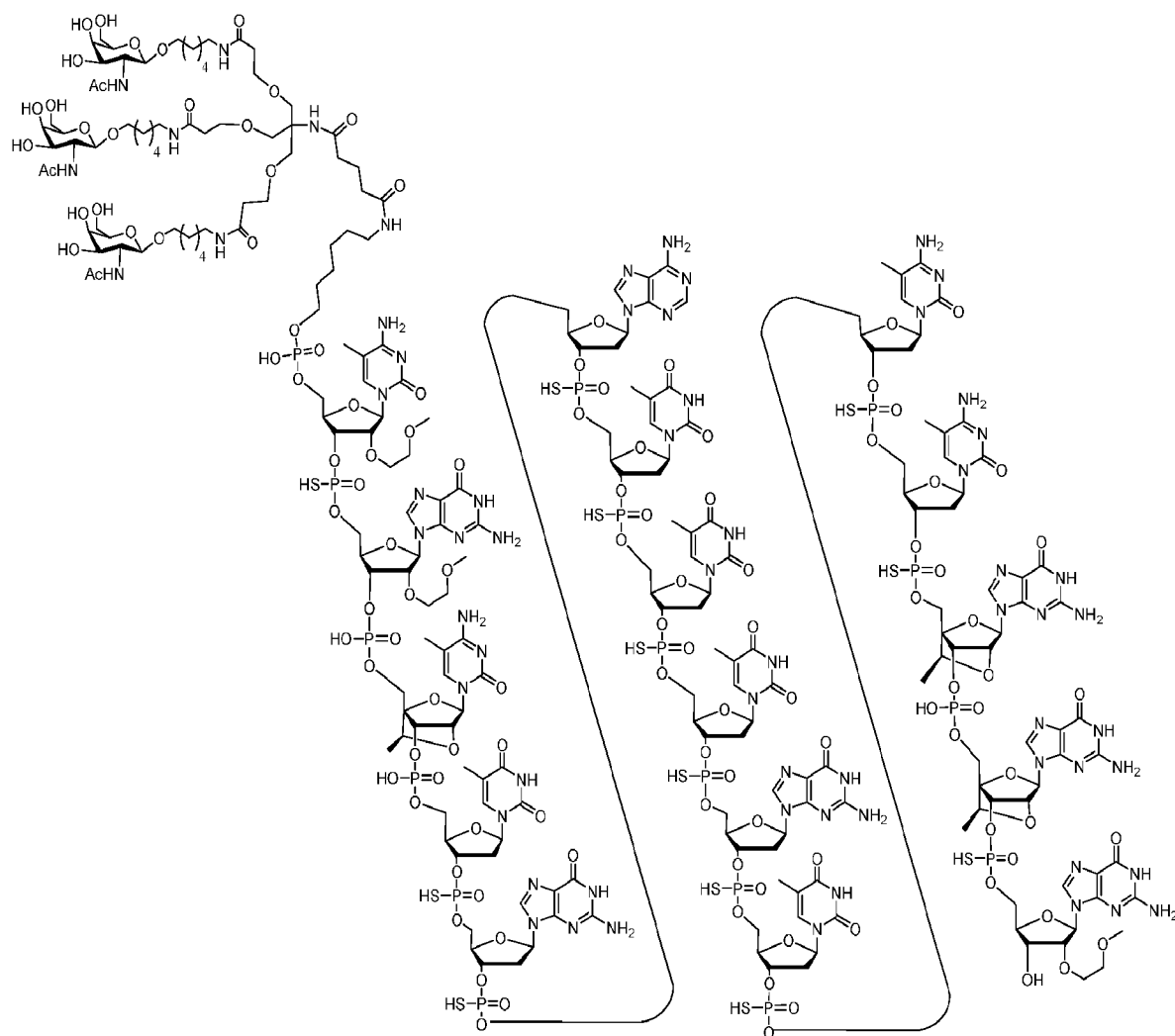
s = a phosphorothioate internucleoside linkage,

o = a phosphodiester internucleoside linkage, and

THA-C6-GalNAc₃=



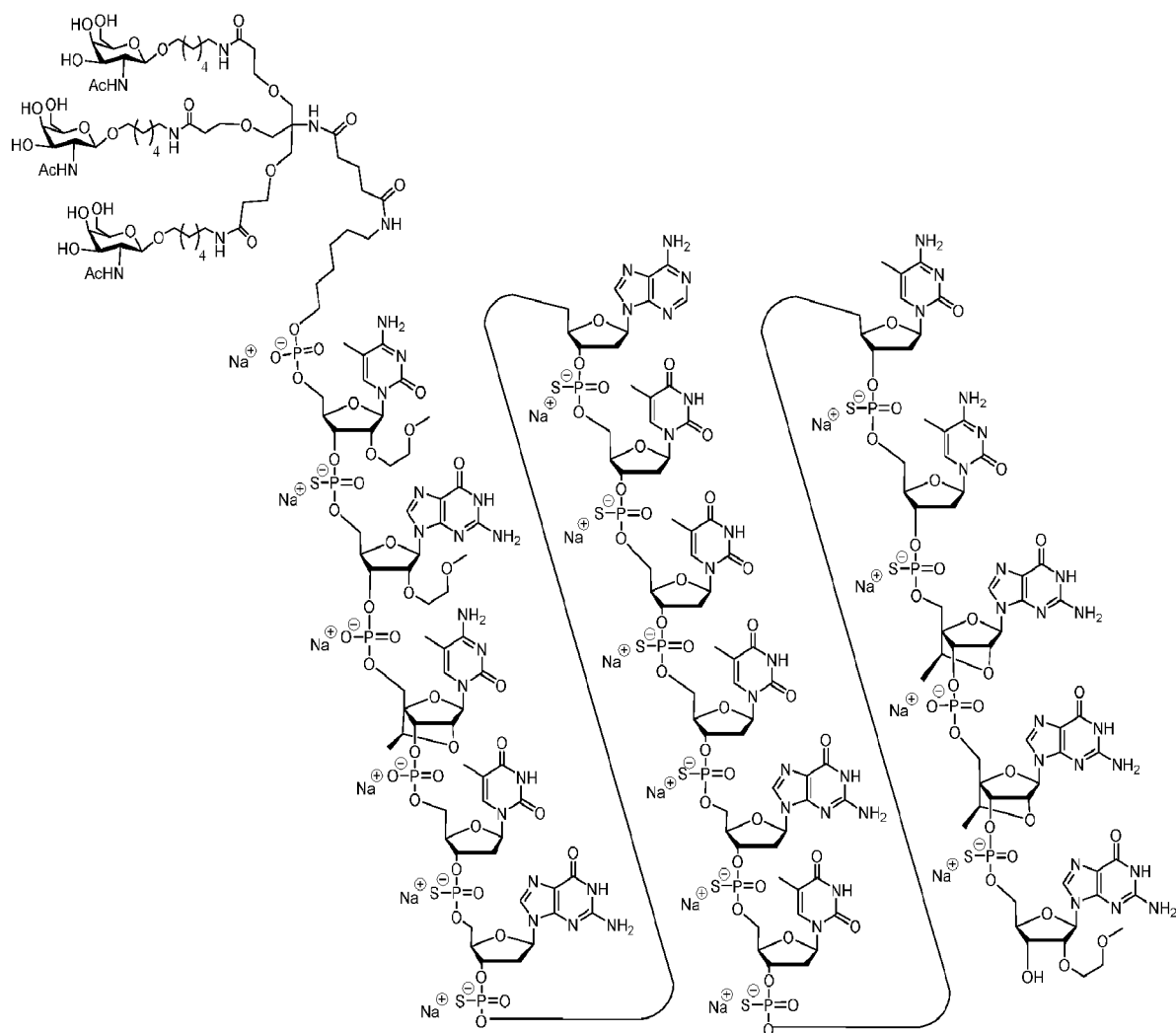
12. The method or use of any one of claims 1-10, wherein the oligomeric compound is represented by the following Structure 1:



(SEQ ID NO: 5) or a salt thereof.

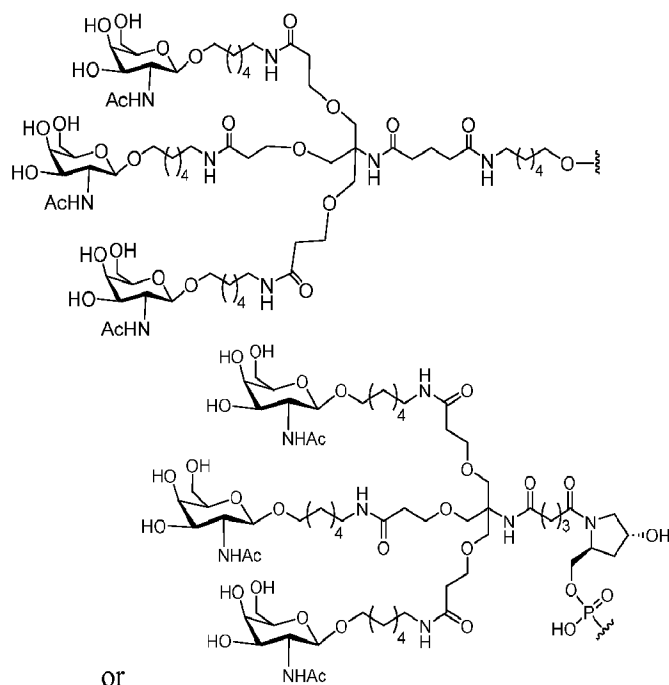
13. The method or use of any one of claims 1-12, wherein the oligomeric compound is a sodium salt or a potassium salt.

14. The method or use of any one of claims 1-10, wherein the oligomeric compound is a sodium salt represented by the following Structure 2:



(SEQ ID NO: 5).

15. The method or use of any one of claims 1-10, wherein the conjugate group comprises the following structure:



16. The method or use of any one of claims 1-10, wherein the conjugate group is attached to the 5'-terminal nucleoside of the modified oligonucleotide or the 3'-terminal nucleoside of the modified oligonucleotide.

17. The method or use of any one of claims 1-16, wherein the amount of AGT protein in the liver of the subject is reduced.

18. The method or use of any one of claims 1-17, wherein the amount of AGT protein in the blood, serum or plasma of the subject is reduced.

19. The method or use of any one of claims 1-6 and 11-18, wherein the subject has or is at risk for, or the heart failure is, heart failure with reduced ejection fraction (HFrEF), heart failure with mid-range ejection fraction (HFmrEF), heart failure with improved ejection fraction (HFimpEF), or heart failure with preserved ejection fraction (HFpEF).

20. The method or use of any one of claims 1-19, wherein the subject has a left ventricular ejection fraction of about 50% or less, about 40% or less, or about 35% or less, or about 30% or less.

21. The method or use of any one of claims 1-20, wherein the subject has one or more of asymptomatic left ventricular dysfunction (ALVD), asymptomatic or symptomatic valvular heart disease, left ventricular hypertrophy, left ventricular fibrosis, left ventricular dilatation, and left ventricular hypocontractility.

22. The method or use of any one of claims 1-21, wherein a decrease in the amount of AGT RNA and/or AGT protein in the subject is less than 95%, or less than 94%, or less than 93%, or less than 92%, or

less than 91%, or less than 90% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric compound or salt thereof.

23. The method or use of any one of claims 1-21, wherein the amount of AGT RNA and/or AGT protein in the subject is decreased by no more than 85%, or no more than 86%, or no more than 87%, or no more than 88%, or no more than 89%, or no more than 90%, or no more than 91%, or no more than 92%, or no more than 93%, or no more than 94%, or no more than 95% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric compound or salt thereof.

24. The method or use of any one of claims 1-21, wherein the amount of AGT RNA and/or AGT protein is decreased by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared to the amount of AGT protein prior to administering the oligomeric compound or salt thereof.

25. The method or use of any one of claims 1-21, wherein the amount of AGT RNA and/or AGT protein is decreased by at least 70%, at least 75%, at least 80% or at least 85% and less than 90% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric compound or salt thereof.

26. The method or use of any one of claims 1-21, wherein the amount of AGT RNA and/or AGT protein in the subject is decreased by at least 75% and less than 95%, less than 94%, less than 93%, less than 92%, less than 91%, less than 90%, less than 89%, less than 88%, or less than 85% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric compound or salt thereof.

27. The method or use of any one of claims 1-26, wherein the oligomeric compound or salt thereof is the only RAAS inhibitor administered to the subject.

28. The method or use of any one of claims 1-26, wherein the subject has been previously treated with a GDMT for heart failure.

29. The method or use of any one of claims 1-26, wherein the subject has been previously treated with a RAAS inhibitor.

30. The method or use of any one of claims 1-26, wherein the subject has been previously treated with an ACE inhibitor, an ARB, an ARNi, a MRA and/or a direct renin inhibitor.

31. The method or use of any one of claims 1-26, wherein the subject is being treated concurrently with a RAAS inhibitor in addition to the oligomeric compound.

32. The method or use of any one of claims 1-26, wherein the subject is being treated concurrently with an ACE inhibitor, ARB an ARNi, a MRA and/or a renin inhibitor.

33. The method of any one of claims 1-26, comprising administering the oligomeric compound or salt thereof and simultaneously or sequentially administering: (i) a RAAS inhibitor or (ii) an ACE inhibitor, ARB, ARNi, MRA or direct renin inhibitor to the subject.

34. The method of claim 33, wherein the oligomeric compound or salt thereof and (i) or (ii) are administered simultaneously in a single composition.

35. The method or use of any one of claims 31-34, wherein the RAAS inhibitor, ACE inhibitor, ARB, ARNi, MRA or a direct renin inhibitor is administered at less than the Guideline-recommended target dose for treatment of HFrEF.

36. The method or use of claim 35, wherein the RAAS inhibitor, ACE inhibitor, ARB, ARNi, MRA or renin inhibitor is administered at less than about 70%, less than about 60%, less than about 50%, or less than about 40% of the Guideline-recommended target dose for treatment of HFrEF.

37. The method or use of any one of claims 28-36, wherein the RAAS inhibitor, ACE inhibitor, ARB, ARNi, MRA or renin inhibitor is administered at a frequency that is less than the Guideline-recommended dosing regimen for treatment of HFrEF.

38. The method or use of any one of claims 1-27, wherein the subject is treated concurrently with a neprilysin inhibitor.

39. The method or use of any one of claims 1-27, further comprising simultaneously or sequentially administering a neprilysin inhibitor to the subject.

40. The method or use of claim 38 or claim 39, wherein the neprilysin inhibitor is sacubitril.

41. The method or use of claim 39 or claim 40, further comprising simultaneously or sequentially administering an ARB to the subject.

42. The method or use of claim 41, wherein the ARB is valsartan.

43. The method or use of any one of claims 1-42, wherein the subject has asymptomatic left ventricular dysfunction (ALVD).

44. The method or use of any one of claims 1-42, wherein the subject has structural and/or functional abnormalities of the pericardium, myocardium and/or a cardiac valve.

45. The method or use of any one of claims 1-42, wherein the subject has one or more of asymptomatic or symptomatic valvular heart disease, left ventricular hypertrophy, left ventricular fibrosis, left ventricular dilatation, and left ventricular hypocontractility.

46. The method or use of any one of claims 1-45, wherein the subject has or is at risk of having angioedema or asthma.

47. The method or use of any one of claims 1-46, wherein the subject has renal insufficiency.

48. The method or use of claim 47, wherein the subject has an estimated glomerular filtration rate (eGFR) of between 30 and 90 ml/min/1.73 m², between 30 and 89 ml/min/1.73 m², between 30 and 80

ml/min/1.73 m², between 20 and 89 ml/min/1.73 m², between 20 and 80 ml/min/1.73 m², between 45 and 89 ml/min/1.73 m², between 40 and 89 ml/min/1.73 m², between 40 and 80 ml/min/1.73 m², between 60 and 89 ml/min/1.73 m², between 30 and 60 ml/min/1.73 m², between 30 and 59 ml/min/1.73 m², between 40 and 60 ml/min/1.73 m², between 30 and 44 ml/min/1.73 m², between 35 and 45 ml/min/1.73 m², between 15 and 44 ml/min/1.73 m², between 15 and 29 ml/min/1.73 m², less than about 90 ml/min/1.73 m², less than about 89 ml/min/1.73 m², less than about 80 ml/min/1.73 m², less than about 70 ml/min/1.73 m², less than about 60 ml/min/1.73 m², less than about 59 ml/min/1.73 m², less than about 45 ml/min/1.73 m², less than about 44 ml/min/1.73 m², less than about 40 ml/min/1.73 m², less than about 30 ml/min/1.73 m², less than about 29 ml/min/1.73 m², or less than about 15 ml/min/1.73 m².

49: The method or use of any one of claims 1-48, wherein administering or use of the oligomeric compound or salt thereof comprises administering or use of a fixed dose of the oligomeric compound or salt thereof within the range of about 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 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 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 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 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 150 mg, 100 mg to 140 mg, 100 mg to 120 mg, 100 mg to 110 mg, 110 mg to 150 mg, 110 mg to 140 mg, 110 mg to 130 mg, 110 mg to 120 mg, 120 mg to 150 mg, 120 mg to 140 mg, 120 mg to 130 mg, 130 mg to 150 mg, 130 mg to 140 mg, 140 mg to 150 mg, 55 mg to 125 mg, 55 mg to 115 mg, 55 mg to 105 mg, 55 mg to 95 mg, 55 mg to 85 mg, 55 mg to 75 mg, 55 mg to 65 mg, 65 mg to 125 mg, 65 mg to 115 mg, 65 mg to 105 mg, or 65 mg to 95 mg, 65 mg to 85 mg, 65 mg to 75 mg, 75 mg to 125 mg, 75 mg to 115 mg, 75 mg to 105 mg, 75 mg to 95 mg, 75 mg to 85 mg, 85 mg to 125 mg, 85 mg to 115 mg, 85 mg to 105 mg, or 85 mg to 95 mg.

50: The method or use of any one of claims 1-48, wherein administering or use of the oligomeric compound or salt thereof comprises administering or use of a fixed dose of the oligomeric compound or salt thereof within the range of about 50 mg to about 150 mg, about 50 mg to about 140 mg, about 50 mg to about 120 mg, about 50 mg to about 110 mg, about 50 mg to about 100 mg, about 50 mg to about 80 mg, about 50 mg to about 70 mg, about 50 mg to about 60 mg, about 60 mg to about 150 mg, about 60 mg to about 140 mg, about 60 mg to about 120 mg, about 60 mg to about 110 mg, about 60 mg to about 100 mg, about 60 mg to about 80 mg, about 60 mg to about 70 mg, about 70 mg to about 150 mg, about 70 mg to about 140 mg, about 70 mg to about 120 mg, about 70 mg to about 110 mg, about 70 mg to about 100 mg, about 70 mg to about 80 mg, about 80 mg to about 150 mg, about 80 mg to about 140 mg, about 80 mg to about 120 mg, about 80 mg to about 110 mg, about 80 mg to about 100 mg, about 80 mg to about 90 mg, about 90 mg to about 150 mg, about 90 mg to about 140 mg, about 90 mg to about 120 mg, about 90 mg to about 110 mg,

about 90 mg to about 100 mg, about 100 mg to about 150 mg, about 100 mg to about 140 mg, about 100 mg to about 120 mg, about 100 mg to about 110 mg, about 110 mg to about 150 mg, about 110 mg to about 140 mg, about 110 mg to about 130 mg, about 110 mg to about 120 mg, about 120 mg to about 150 mg, about 120 mg to about 140 mg, about 120 mg to about 130 mg, about 130 mg to about 150 mg, about 130 mg to about 140 mg, about 140 mg to about 150 mg, about 55 mg to about 125 mg, about 55 mg to about 115 mg, about 55 mg to about 105 mg, about 55 mg to about 95 mg, about 55 mg to about 85 mg, about 55 mg to about 75 mg, about 55 mg to about 65 mg, about 65 mg to about 125 mg, about 65 mg to about 115 mg, about 65 mg to about 105 mg, or about 65 mg to about 95 mg, about 65 mg to about 85 mg, about 65 mg to about 75 mg, about 75 mg to about 125 mg, about 75 mg to about 115 mg, about 75 mg to about 105 mg, about 75 mg to about 95 mg, about 75 mg to about 85 mg, about 85 mg to about 125 mg, about 85 mg to about 115 mg, about 85 mg to about 105 mg, or about 85 mg to about 95 mg.

51. The method or use of any one of claims 1-48, wherein administering or use of the oligomeric compound or salt thereof comprises administering or use of a fixed dose of at least about 50 mg and less than about 150 mg, at least about 50 mg and less than about 145 mg, at least about 50 mg and less than about 140 mg, at least about 50 mg and less than about 135 mg, at least about 50 mg and less than about 130 mg, at least about 50 mg and less than about 125 mg, at least about 50 mg and less than about 120 mg, at least about 50 mg and less than about 115 mg, at least about 50 mg and less than about 110 mg, at least about 50 mg and less than about 105 mg, at least about 50 mg and less than about 100 mg, at least about 50 mg and less than about 95 mg, at least about 50 mg and less than about 90 mg, at least about 50 mg and less than about 85 mg, at least about 50 mg and less than about 80 mg, at least about 50 mg and less than about 75 mg, at least about 50 mg and less than about 70 mg, at least about 50 mg and less than about 65 mg, at least about 55 mg and less than about 65 mg, at least about 60 mg and less than about 150 mg, at least about 60 mg and less than about 145 mg, at least about 60 mg and less than about 140 mg, at least about 60 mg and less than about 135 mg, at least about 60 mg and less than about 130 mg, at least about 60 mg and less than about 125 mg, at least about 60 mg and less than about 120 mg, at least about 60 mg and less than about 115 mg, at least about 60 mg and less than about 110 mg, at least about 60 mg and less than about 105 mg, at least about 60 mg and less than about 100 mg, at least about 60 mg and less than about 95 mg, at least about 70 mg and less than about 150 mg, at least about 70 mg and less than about 145 mg, at least about 70 mg and less than about 140 mg, at least about 70 mg and less than about 135 mg, at least about 70 mg and less than about 130 mg, at least about 70 mg and less than about 125 mg, at least about 70 mg and less than about 120 mg, at least about 70 mg and less than about 115 mg, at least about 70 mg and less than about 110 mg, at least about 70 mg and less than about 105 mg, at least about 70 mg and less than about 100 mg, at least about 70 mg and less than about 95 mg, at least about 80 mg and less than about 150 mg, at least about 80 mg and less than about 145 mg, at least about 80 mg and less than about 140 mg, at least about 80 mg and less than about 135 mg, at least

about 80 mg and less than about 130 mg, at least about 80 mg and less than about 125 mg, at least about 80 mg and less than about 120 mg, at least about 80 mg and less than about 115 mg, at least about 80 mg and less than about 110 mg, at least about 80 mg and less than about 105 mg, at least about 80 mg and less than about 100 mg, at least about 80 mg and less than about 95 mg, or at least about 85 mg and less than about 95 mg of the oligomeric compound or salt thereof.

52. The method or use of any one of claims 1-48, wherein administering or use of the oligomeric compound or salt thereof comprises administering or use of a fixed dose of 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, or about 150 mg of the oligomeric compound or salt thereof.

53. The method or use of any one of claims 1-48, wherein administering or use of the oligomeric compound or salt thereof comprises administering or use of a fixed dose of 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, or 150 mg of the oligomeric compound or salt thereof.

54. The method or use of any one of claims 1-48, wherein administering or use comprises administering or use of a fixed dose of about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, or about 100 mg of the oligomeric compound or salt thereof.

55. The method or use of any one of claims 1-48, wherein the administering or use comprises administering or use of a fixed dose of 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, or 100 mg of the oligomeric compound or salt thereof.

56. The method or use of any one of claims 1-48, wherein the administering or use comprises administering or use of a fixed dose of the oligomeric compound or salt thereof within the range of about 55 mg to about 100 mg, about 60 mg to about 100 mg, about 65 mg to about 100 mg, about 70 mg to about 100 mg, about 75 mg to about 100 mg, about 80 mg to about 100 mg, about 85 mg to about 100 mg, about 85 mg to about 100 mg, or about 85 mg to about 95 mg.

57. The method or use of any one of claims 1-48, comprising administering or use of a fixed dose of about 55 mg of the oligomeric compound or salt thereof.

58. The method or use of any one of claims 1-48, comprising administering or use of a fixed dose of about 60 mg of the oligomeric compound or salt thereof.

59. The method or use of any one of claims 1-48, comprising administering or use of a fixed dose of about 65 mg of the oligomeric compound or salt thereof.

60. The method or use of any one of claims 1-48, comprising administering or use of a fixed dose of about 70 mg of the oligomeric compound or salt thereof.

61. The method or use of any one of claims 1-48, comprising administering or use of a fixed dose of about 75 mg of the oligomeric compound or salt thereof.

62. The method or use of any one of claims 1-48, comprising administering or use of a fixed dose of about 80 mg of the oligomeric compound or salt thereof.

63. The method or use of any one of claims 1-48, comprising administering or use of a fixed dose of about 85 mg of the oligomeric compound or salt thereof.

64. The method or use of any one of claims 1-48, comprising administering or use of a fixed dose of about 90 mg of the oligomeric compound or salt thereof.

65. The method or use of any one of claims 1-48, comprising administering or use of a fixed dose of about 95 mg of the oligomeric compound or salt thereof.

66. The method or use of any one of claims 1-48, comprising administering or use of a fixed dose of about 100 mg of the oligomeric compound or salt thereof.

67. The method or use of any one of claims 1-48, comprising administering or use of a fixed dose of 55 mg to 105 mg of the oligomeric compound or salt thereof.

68. The method or use of any one of claims 1-48, comprising administering or use of a unit dose of 60 mg of the oligomeric compound or salt thereof.

69. The method or use of any one of claims 1-48, comprising administering or use of a fixed dose of 65 mg of the oligomeric compound or salt thereof.

70. The method or use of any one of claims 1-48, comprising administering or use of a fixed dose of 70 mg of the oligomeric compound or salt thereof.

71. The method or use of any one of claims 1-48, comprising administering or use of a fixed dose of 75 mg of the oligomeric compound or salt thereof.

72. The method or use of any one of claims 1-48, comprising administering or use of a fixed dose of 80 mg of the oligomeric compound or salt thereof.

73. The method or use of any one of claims 1-48, comprising administering or use of a fixed dose of 85 mg of the oligomeric compound or salt thereof.

74. The method or use of any one of claims 1-48, comprising administering or use of a fixed dose of 90 mg of the oligomeric compound or salt thereof.

75. The method or use of any one of claims 1-48, comprising administering or use of a fixed dose of 95 mg of the oligomeric compound or salt thereof.

76. The method or use of any one of claims 1-48, comprising administering or use of a fixed dose of 100 mg of the oligomeric compound or salt thereof.

77. The method or use of any one of claims 1-48, wherein the oligomeric compound or salt thereof is ION904 or a salt thereof.

78. The method of any one of claims 1-77, wherein the oligomeric compound or salt thereof is administered once about every 4 weeks or once about every 28 days.

79. The method of any one of claims 1-77, wherein the oligomeric compound or salt thereof is administered at an interval of about once a month, about once every two months, or about once every three months.

80. The method of any one of claims 1-77, wherein the oligomeric compound or salt thereof is administered about once every 2 weeks, about once every 3 weeks, about once every 4 weeks, about once every 5 weeks, about once every 6 weeks, about once every 7 weeks, about once every 8 weeks, about once every 9 weeks, or about once every 10 weeks.

81. The method of any one of claims 1-77, wherein the oligomeric compound or salt thereof is administered once every 4 weeks or once every 28 days.

82. The method of any one of claims 1-77, wherein the oligomeric compound or salt thereof is administered at an interval of once a month, once every two months, or once every three months.

83. The method of any one of claims 1-77, wherein the oligomeric compound or salt thereof is administered once every 2 weeks, once every 3 weeks, once every 4 weeks, once every 5 weeks, once every 6 weeks, once every 7 weeks, once every 8 weeks, once every 9 weeks, or once every 10 weeks.

84. The method or use of any one of claims 1-83, wherein administering or use comprises administering or use of a fixed dose of 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, or 100 mg of the oligomeric compound or salt thereof once every 3 weeks, once every 4 weeks, once every 5 weeks or once every 6 weeks.

85. The method or use of any one of claims 1-83, wherein administering or use comprises administering or use of a fixed dose of about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, or about 100 mg of the oligomeric compound or salt thereof once about every 3 weeks, once about every 4 weeks, once about every 5 weeks or once about every 6 weeks, wherein the oligomeric compound is formulated for parenteral administration.

86. The method or use of claim 85, wherein administering or use comprises administering or use of a fixed dose of about 60 mg, about 70 mg, about 80 mg, about 90 mg, or about 100 mg of the oligomeric compound or salt thereof once about every 25 days, once about every 26 days, once about every 27 days, once about every 28 days, once about every 29 days, once about every 30 days, or once about every 31 days, wherein the oligomeric compound is formulated for parenteral administration.

87. The method or use of claim 85, wherein administering or use comprises administering or use of a fixed dose of 60 mg or about 60 mg, or 90 mg or about 90 mg of the oligomeric compound or salt thereof once every 28 days or about every 28 days, or once every 4 weeks or about every 4 weeks, or once a month or about once a month, wherein the oligomeric compound is formulated for subcutaneous administration.

88. The method or use of claim 85, wherein administering or use comprises administering or use of a fixed dose of about 60 mg or about 90 mg of the oligomeric compound or salt thereof once about every 28 days or once about every 4 weeks, or once about every month, wherein the oligomeric compound is formulated for subcutaneous administration.

89. The method or use of any one of claims 1-88, wherein the oligomeric compound or salt thereof comprises administering or use of a loading dose.

90. The method or use of claim 89, wherein the administering or use comprises one or more maintenance doses of the oligomeric compound or salt thereof.

91. The method or use of claim 90, wherein the loading dose comprises a greater amount of the oligomeric compound or salt thereof than a maintenance dose.

92. The method or use of claim 90, wherein the loading dose and the maintenance dose comprises the same amount of the oligomeric compound or salt thereof.

93. The method or use of any one of claims 1-92, wherein the administration or use of the oligomeric compound or salt thereof is effective to decrease the amount of AGT RNA and/or AGT protein in the subject by at least 70%, at least 75%, at least 80%, or at least 85% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration or use of the oligomeric compound or salt thereof.

94. The method or use of any one of claims 1-93, wherein such method or use is effective to treat heart failure and/or ameliorate one or more symptoms of heart failure, but does not significantly reduce systolic blood pressure and/or diastolic blood pressure in a subject having, or at risk for, heart failure.

95. The method or use of any one of claims 1-93, wherein such method or use improves cardiac function, reduces cardiac dilation, reduces cardiac fibrosis, reverses or attenuates cardiac remodeling, increases LVEF, improves left ventricular end systolic volume (LVESV) or left ventricular indexed end systolic volume (LVESVi), improves left ventricular end diastolic volume (LVEDV), improves left ventricle (LV) strain, improves 6-minute walk test, and/or improves quality of life in the subject having, or at risk for, heart failure.

96. The method or use of any one of claims 1-93, wherein such method or use decreases the level of NT-proBNP, BNP, high-sensitive cardiac troponin T (hs-cTnT), and/or cTnT in blood, plasma, or serum of the subject having, or at risk for, heart failure

97. The method or use of any one of claims 1-93, wherein such method or use ameliorates at least one symptom of heart failure selected from fatigue, rapid or irregular heartbeat, palpitation, shortness of breath, chest pain, dizziness, weakness, dyspnea, orthopnea, edema, hepatic congestion, or ascites in the subject having, or at risk for, heart failure.

98. The method or use of any one of claims 1-93, wherein such method or use slows or prevents progression of one or more symptoms or signs of heart failure in the subject having, or at risk for, heart failure.

99. The method or use of any one of claims 1-93, wherein such method or use improves or eliminates one or more symptoms or signs of heart failure in the subject having, or at risk for, heart failure.

100. The method or use of any one of claims 1-99, wherein the oligomeric compound or salt thereof is administered in a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

101. The method or use of claim 100, wherein the pharmaceutical composition comprises water, saline, or 2mM phosphate buffered isotonic saline, pH 7.4.

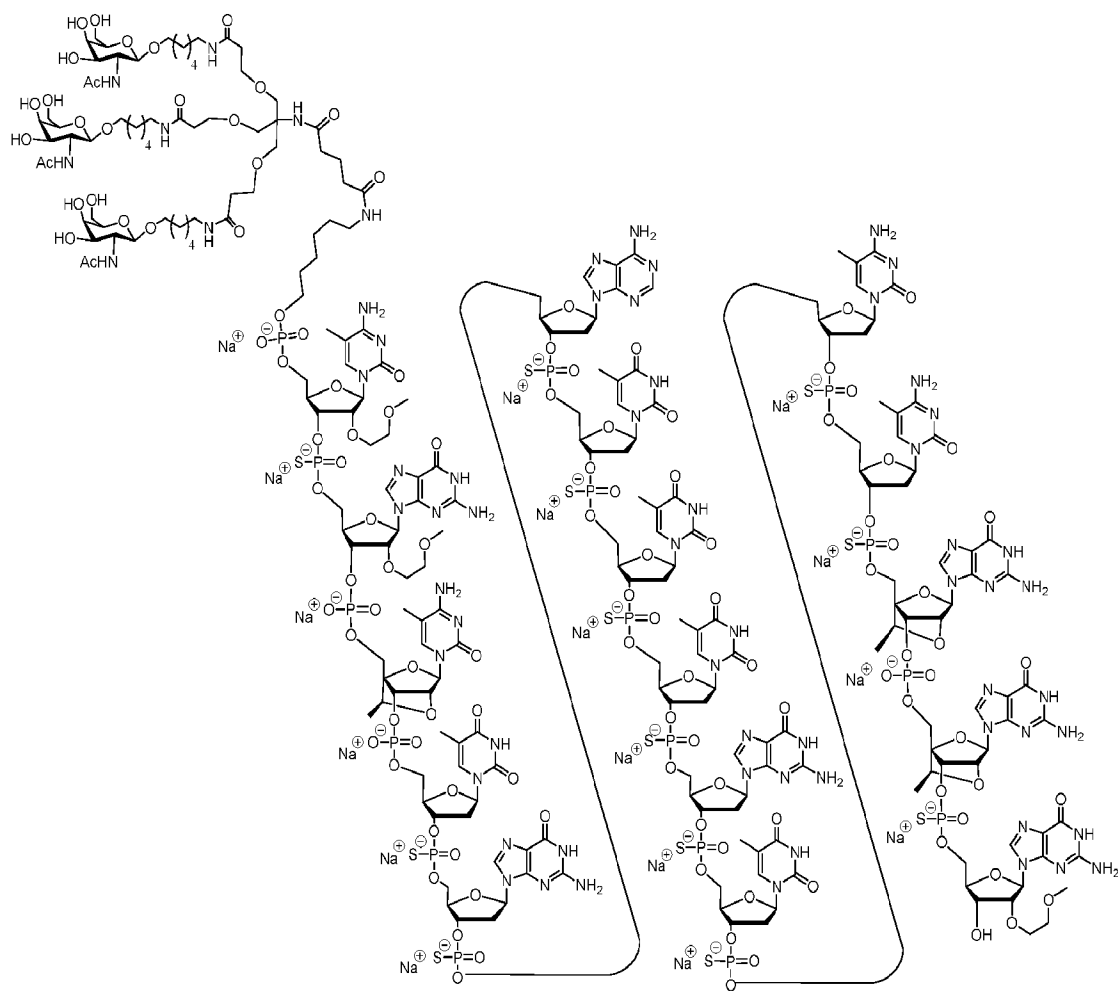
102. The method or use of any one of claims 1-101, wherein the oligomeric compound or salt thereof, or pharmaceutical composition is administered parenterally.

103. The method or use of claim 102, wherein the oligomeric compound or salt thereof, or pharmaceutical composition is administered subcutaneously.

104. The method or use of claim 103 wherein the oligomeric compound or salt thereof, or pharmaceutical composition is administered by a syringe.

105. The method or use of claim 103, wherein the oligomeric compound or salt thereof, or pharmaceutical composition is administered by an autoinjector device.

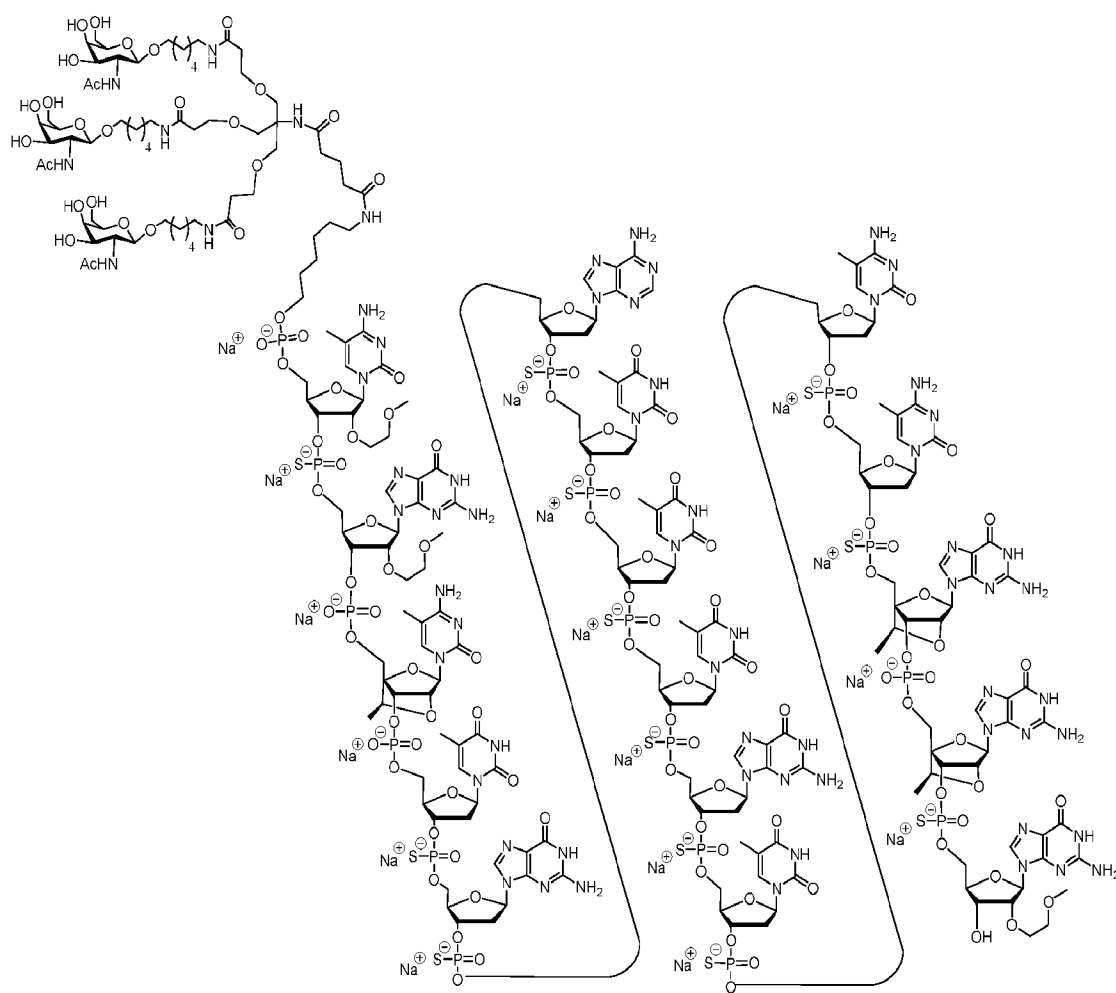
106. A method of treating heart failure in a subject, comprising administering a fixed dose of 55 mg to 100 mg of an oligomeric compound or a salt thereof to a subject; wherein administering the oligomeric compound results in amelioration of one or more symptoms and/or lack of progression of heart failure; wherein the oligomeric compound is represented by the following sodium salt:



(SEQ ID

NO: 5), wherein the oligomeric compound is formulated with a pharmaceutically acceptable carrier or excipient selected from sterile water or sterile saline or phosphate buffered saline, formulated for parenteral administration.

107. Use of a fixed dose of 55 mg to 100 mg of an oligomeric compound or a salt thereof for reducing AGT RNA and/or AGT protein in a subject intolerant, or at risk of being intolerant, to treatment with a renin-angiotensin-aldosterone system (RAAS) inhibitor; wherein the oligomeric compound is compound represented by the following sodium salt:



NO: 5), and wherein the oligomeric compound is formulated with a pharmaceutically acceptable carrier or excipient selected from sterile water or sterile saline or phosphate buffered saline, formulated for parenteral administration.

108. The method of claim 106 or the use of claim 107, wherein the fixed dose is formulated for subcutaneous administration and contained in a single use vial, pre-filled syringe or an autoinjector device.

109. A unit dose comprising 50 mg to 200 mg of an oligomeric compound comprising a GalNAc-conjugated modified oligonucleotide represented by the following chemical notation (5' to 3'):

${}^m\text{C}_{\text{es}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{ko}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{G}_{\text{ko}}\text{G}_{\text{ks}}\text{G}_{\text{e}}$ (SEQ ID NO: 4) or a salt thereof; wherein:

A = an adenine nucleobase,

${}^m\text{C}$ = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

k = a cEt sugar moiety,

d = an unmodified DNA sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage;

and wherein GalNAc is an N-acetyl galactosamine conjugate moiety.

110. A unit dose comprising 50 mg to 150 mg of an oligomeric compound represented by the following chemical notation (5' to 3'):

THA-C6-GalNAc₃-^mC_{es}G_{eo}^mC_{ko}T_{ds}G_{ds}A_{ds}T_{ds}T_{ds}T_{ds}G_{ds}T_{ds}^mC_{ds}^mC_{ds}G_{ko}G_{ks}G_e (SEQ ID NO: 5) or a salt thereof; 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,

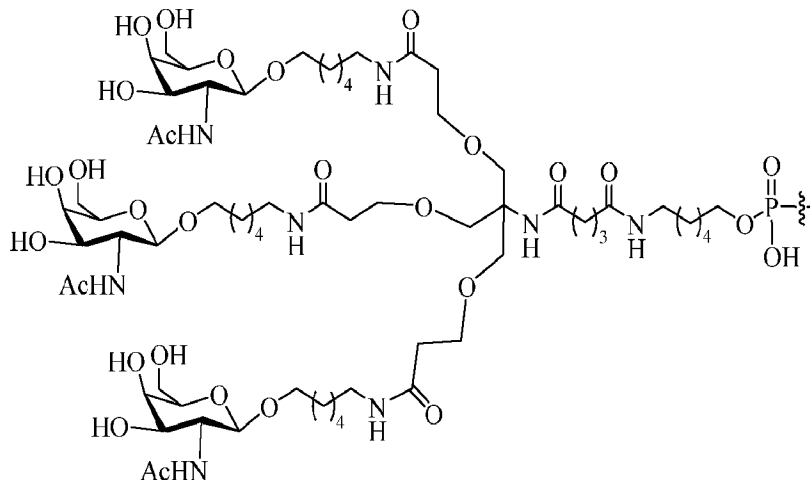
k = a cEt sugar moiety,

d = an unmodified DNA sugar moiety,

s = a phosphorothioate internucleoside linkage,

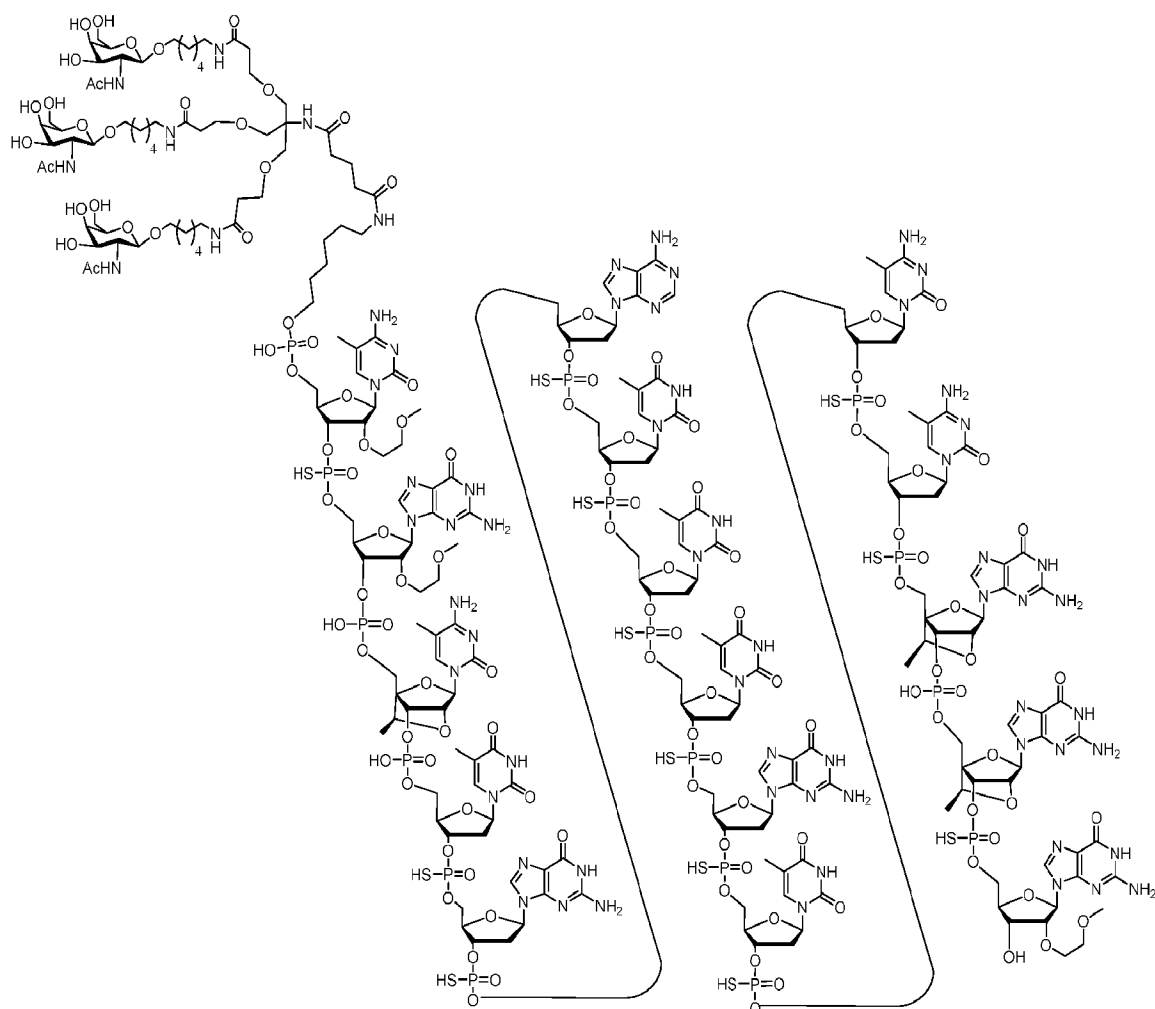
o = a phosphodiester internucleoside linkage, and

THA-C6-GalNAc₃=



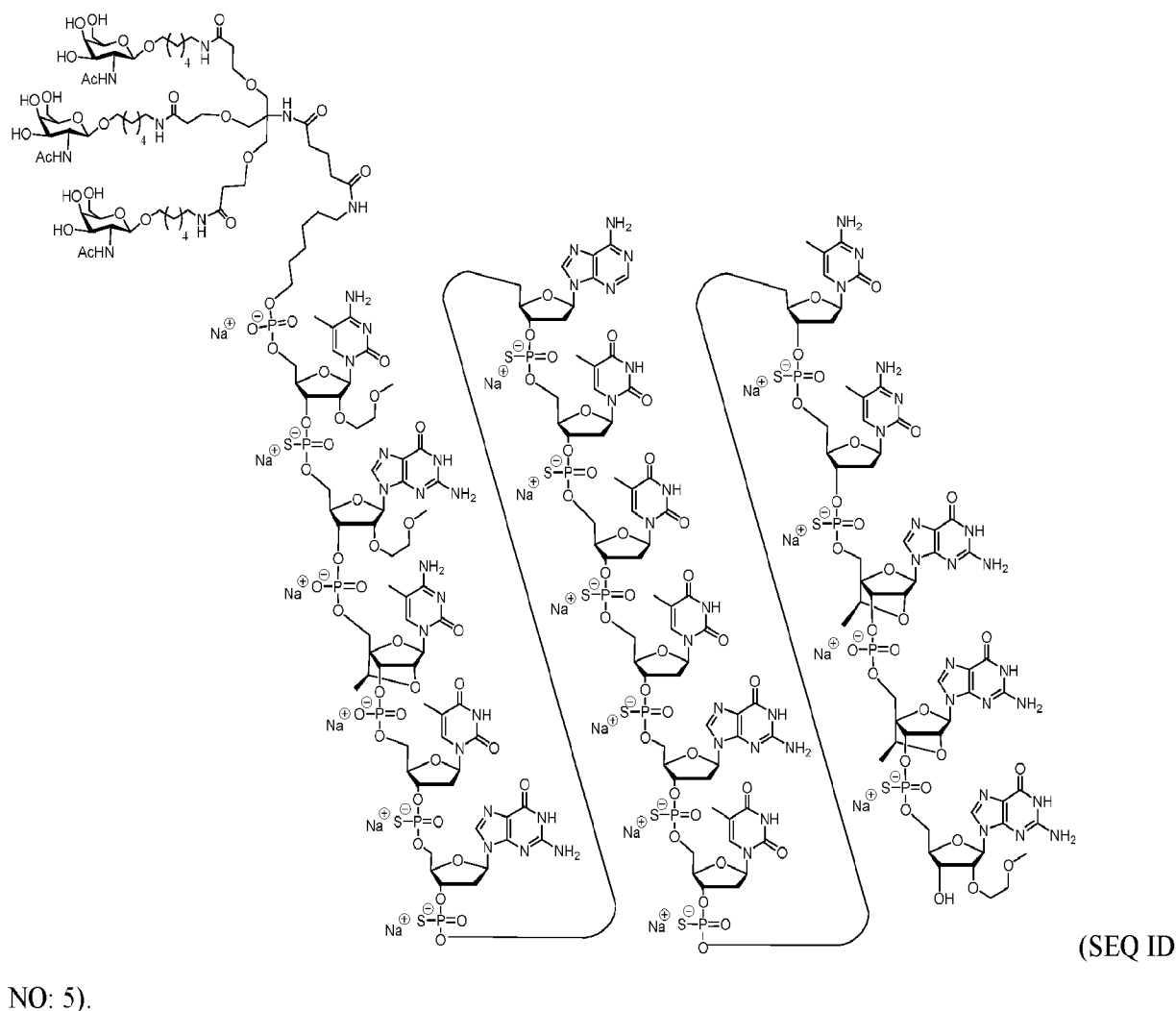
111. A unit dose comprising 50 mg to 150 mg of an oligomeric compound represented by the following

Structure 1:



(SEQ ID NO: 5) or a salt thereof.

112. A unit dose comprising 50 mg to 150 mg an oligomeric compound represented by the following sodium salt Structure 2:



113: The unit dose of any one of claims 109-112, comprising an amount of the oligomeric compound or salt thereof within the range of about 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 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 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 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 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 150 mg, 100 mg to 140 mg, 100 mg to 120 mg, 100 mg to 110 mg, 110 mg to 150 mg, 110 mg to 140 mg, 110 mg to 130 mg, 110 mg to 120 mg, 120 mg to 150 mg, 120 mg to 140 mg, 120 mg to 130 mg, 130 mg to 150 mg, 130 mg to 140 mg, 140 mg to 150 mg, 55 mg to 125 mg, 55 mg to 115 mg, 55 mg to 105 mg, 55 mg to 95 mg, 55 mg to 85 mg, 55 mg to 75 mg, 55 mg to 65 mg, 65 mg to 125 mg, 65 mg to 115 mg, 65 mg to 105 mg, or 65 mg to

95 mg, 65 mg to 85 mg, 65 mg to 75 mg, 75 mg to 125 mg, 75 mg to 115 mg, 75 mg to 105 mg, 75 mg to 95 mg, 75 mg to 85 mg, 85 mg to 125 mg, 85 mg to 115 mg, 85 mg to 105 mg, or 85 mg to 95 mg.

114: The unit dose of any one of claims 109-112, comprising an amount of the oligomeric compound or salt thereof within the range of about 50 mg to about 150 mg, about 50 mg to about 140 mg, about 50 mg to about 120 mg, about 50 mg to about 110 mg, about 50 mg to about 100 mg, about 50 mg to about 80 mg, about 50 mg to about 70 mg, about 50 mg to about 60 mg, about 60 mg to about 150 mg, about 60 mg to about 140 mg, about 60 mg to about 120 mg, about 60 mg to about 110 mg, about 60 mg to about 100 mg, about 60 mg to about 80 mg, about 60 mg to about 70 mg, about 70 mg to about 150 mg, about 70 mg to about 140 mg, about 70 mg to about 120 mg, about 70 mg to about 110 mg, about 70 mg to about 100 mg, about 70 mg to about 80 mg, about 80 mg to about 150 mg, about 80 mg to about 140 mg, about 80 mg to about 120 mg, about 80 mg to about 110 mg, about 80 mg to about 100 mg, about 80 mg to about 90 mg, about 90 mg to about 150 mg, about 90 mg to about 140 mg, about 90 mg to about 120 mg, about 90 mg to about 110 mg, about 90 mg to about 100 mg, about 100 mg to about 150 mg, about 100 mg to about 140 mg, about 100 mg to about 120 mg, about 100 mg to about 110 mg, about 110 mg to about 150 mg, about 110 mg to about 140 mg, about 110 mg to about 130 mg, about 110 mg to about 120 mg, about 120 mg to about 150 mg, about 120 mg to about 140 mg, about 120 mg to about 130 mg, about 130 mg to about 150 mg, about 130 mg to about 140 mg, about 140 mg to about 150 mg, about 55 mg to about 125 mg, about 55 mg to about 115 mg, about 55 mg to about 105 mg, about 55 mg to about 95 mg, about 55 mg to about 85 mg, about 55 mg to about 75 mg, about 55 mg to about 65 mg, about 65 mg to about 125 mg, about 65 mg to about 115 mg, about 65 mg to about 105 mg, or about 65 mg to about 95 mg, about 65 mg to about 85 mg, about 65 mg to about 75 mg, about 75 mg to about 125 mg, about 75 mg to about 115 mg, about 75 mg to about 105 mg, about 75 mg to about 95 mg, about 75 mg to about 85 mg, about 85 mg to about 125 mg, about 85 mg to about 115 mg, about 85 mg to about 105 mg, or about 85 mg to about 95 mg.

115: The unit dose of any one of claims 109-112, comprising at least about 50 mg and less than about 150 mg, at least about 50 mg and less than about 145 mg, at least about 50 mg and less than about 140 mg, at least about 50 mg and less than about 135 mg, at least about 50 mg and less than about 130 mg, at least about 50 mg and less than about 125 mg, at least about 50 mg and less than about 120 mg, at least about 50 mg and less than about 115 mg, at least about 50 mg and less than about 110 mg, at least about 50 mg and less than about 105 mg, at least about 50 mg and less than about 100 mg, at least about 50 mg and less than about 95 mg, at least about 50 mg and less than about 90 mg, at least about 50 mg and less than about 85 mg, at least about 50 mg and less than about 80 mg, at least about 50 mg and less than about 75 mg, at least about 50 mg and less than about 70 mg, at least about 50 mg and less than about 65 mg, at least about 55 mg and less than about 65 mg, at least about 60 mg and less than about 150 mg, at least about 60 mg and less than about 145 mg, at least about 60 mg and less than about 140 mg, at least about 60 mg and less than about 135

mg, at least about 60 mg and less than about 130 mg, at least about 60 mg and less than about 125 mg, at least about 60 mg and less than about 120 mg, at least about 60 mg and less than about 115 mg, at least about 60 mg and less than about 110 mg, at least about 60 mg and less than about 105 mg, at least about 60 mg and less than about 100 mg, at least about 60 mg and less than about 95 mg, at least about 70 mg and less than about 150 mg, at least about 70 mg and less than about 145 mg, at least about 70 mg and less than about 140 mg, at least about 70 mg and less than about 135 mg, at least about 70 mg and less than about 130 mg, at least about 70 mg and less than about 125 mg, at least about 70 mg and less than about 120 mg, at least about 70 mg and less than about 115 mg, at least about 70 mg and less than about 110 mg, at least about 70 mg and less than about 105 mg, at least about 70 mg and less than about 100 mg, at least about 70 mg and less than about 95 mg, at least about 80 mg and less than about 150 mg, at least about 80 mg and less than about 145 mg, at least about 80 mg and less than about 140 mg, at least about 80 mg and less than about 135 mg, at least about 80 mg and less than about 130 mg, at least about 80 mg and less than about 125 mg, at least about 80 mg and less than about 120 mg, at least about 80 mg and less than about 115 mg, at least about 80 mg and less than about 110 mg, at least about 80 mg and less than about 105 mg, at least about 80 mg and less than about 100 mg, at least about 80 mg and less than about 95 mg, or at least about 85 mg and less than about 95 mg of the oligomeric compound or salt thereof.

116. The unit dose of any one of claims 109-112, comprising 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, or about 150 mg of the oligomeric compound or salt thereof.

117. The unit dose of any one of claims 109-112, comprising 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, or 150 mg of the oligomeric compound or salt thereof.

118. The unit dose of any one of claims 109-112, comprising about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, or about 100 mg of the oligomeric compound or salt thereof.

119. The unit dose of any one of claims 109-112, comprising 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, or 100 mg of the oligomeric compound or salt thereof.

120. The unit dose of any one of claims 109-112, comprising an amount of the oligomeric compound or salt thereof within the range of about 55 mg to about 100 mg, about 60 mg to about 100 mg, about 65 mg to about 100 mg, about 70 mg to about 100 mg, about 75 mg to about 100 mg, about 80 mg to about 100 mg, about 85 mg to about 100 mg, about 85 mg to about 100 mg, or about 85 mg to about 95 mg.

121. The unit dose of any one of claims 109-112, comprising about 55 mg of the oligomeric compound or salt thereof.

122. The unit dose of any one of claims 109-112, comprising about 60 mg of the oligomeric compound or salt thereof.

123. The unit dose of any one of claims 109-112, comprising about 65 mg of the oligomeric compound or salt thereof.

124. The unit dose of any one of claims 109-112, comprising about 70 mg of the oligomeric compound or salt thereof.

125. The unit dose of any one of claims 109-112, comprising about 75 mg of the oligomeric compound or salt thereof.

126. The unit dose of any one of claims 109-112, comprising about 80 mg of the oligomeric compound or salt thereof.

127. The unit dose of any one of claims 109-112, comprising about 85 mg of the oligomeric compound or salt thereof.

128. The unit dose of any one of claims 109-112, comprising about 90 mg of the oligomeric compound or salt thereof.

129. The unit dose of any one of claims 109-112, comprising about 95 mg of the oligomeric compound or salt thereof.

130. The unit dose of any one of claims 109-112, comprising about 100 mg of the oligomeric compound or salt thereof.

131. The unit dose of any one of claims 109-112, comprising 55 mg to 95 mg of the oligomeric compound or salt thereof.

132. The unit dose of any one of claims 109-131, further comprising a neprilysin inhibitor.

133. The unit dose of claim 132, wherein the neprilysin inhibitor is sacubitril.

134. The unit dose of any one of claims 109-133, further comprising an ACEi, ARB, ARNi or MRA.

135. The unit dose of any claim 132 or claim 133, further comprising an ARB which is valsartan.

136. The unit dose of claim 134 or claim 135, wherein the dose of the ACEi, ARB, ARNi or MRA is lower than the Guideline-recommended, target dose for treating HFrEF.

137. The unit dose of claim 136, wherein the dose of the ACEi, ARB, ARNi or MRA is less than about 80%, 70%, 60%, 55%, 50%, 45%, or 40% of the Guideline-recommended target dose for treating HFrEF.

138. The unit dose of any one of claims 109-131, wherein the unit dose does not contain any other RAAS inhibitor.

139. The unit dose of any one of claims 109-138, further comprising a pharmaceutically acceptable carrier, adjuvant or excipient.

140. The unit dose of claims 139, consisting of the oligomeric compound or salt thereof and a pharmaceutically acceptable carrier or excipient.

141. The unit dose of claim 139, wherein the pharmaceutically acceptable carrier or excipient is sterile water or sterile saline or phosphate buffered saline.

142. The unit dose of claim 141, consisting of the oligomeric compound or salt thereof and sterile water or sterile saline or phosphate buffered saline.

143. The unit dose of any one of claims 109-142, formulated for parenteral administration.

144. The unit dose of claim 143, formulated for subcutaneous, intramuscular, or intravenous administration.

145. The unit dose of claim 143, formulated for subcutaneous administration.

146. The unit dose of any one of claims 109-145, contained in a single-dose vial.

147. The unit dose of any one of claims 109-145, provided in multi-dose vials.

148. The unit dose of any one of claims 109-145, contained in a prefilled syringe.

149. The unit dose of any one of claims 109-145, contained in a single-dose prefilled syringe.

150. The unit dose of any one of claims 109-145, contained in an autoinjector device.

151. A kit, comprising:

- (a) the unit dose of any one of claims 109-150, and
- (b) instructions for use, and, optionally,
- (c) means for administering the unit dose.

152. The kit of claim 151, wherein the instructions are for use in reducing the amount of AGT RNA and/or AGT protein in a subject having or at risk for heart failure.

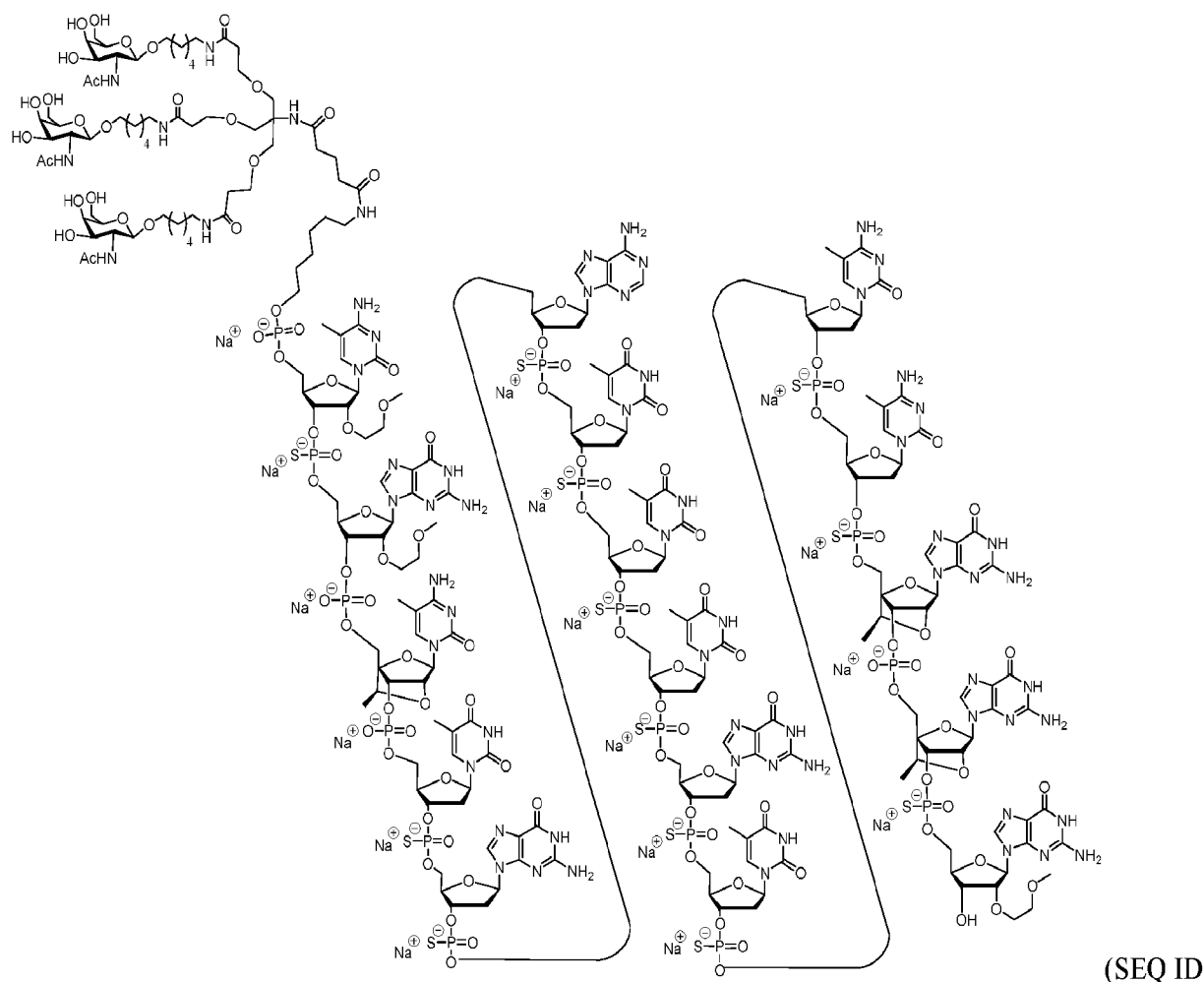
153. The kit of claim 151, wherein the instructions are for use in treating, or ameliorating one or more symptoms of, heart failure in a subject having or at risk for heart failure.

154. The method or use or unit dose of any one of claims 1-153, wherein the modified oligonucleotide is single-stranded.

155. The method or use or unit dose of any one of claims 1-153, wherein the modified oligonucleotide is the only oligonucleotide in the oligomeric compound.

156. The method or use or unit dose of any one of claims 1-153, wherein the modified oligonucleotide is double-stranded.

157. A unit dose comprising 55 mg to 100 mg of an oligomeric compound represented by the following sodium salt:



NO: 5), and a pharmaceutically acceptable carrier or excipient selected from sterile water or sterile saline or phosphate buffered saline, formulated for parenteral administration.

158. The unit dose of claim 157, formulated for subcutaneous administration and contained in a single use vial, pre-filled syringe or an autoinjector device.

159. A method for reducing the amount of angiotensinogen (AGT) RNA and/or AGT protein in a subject who is or is at risk of being intolerant to treatment with a renin-angiotensin-aldosterone system (RAAS) inhibitor, comprising administering about 15 mg to about 200 mg of an oligomeric agent or salt thereof to a subject having or at risk for heart failure, wherein the oligomeric agent comprises a modified oligonucleotide consisting of 16-30 linked nucleosides, and wherein the modified oligonucleotide comprises a nucleobase sequence of at least 16 contiguous nucleosides at least 80% complementary to the nucleobase sequence of an equal length region of nucleobases 2046-2061 of SEQ ID NO: 1 or nucleobases 14940-14955 of SEQ ID NO: 2; wherein:

the amount of AGT RNA and/or AGT protein in the subject is decreased by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent.

160. A method of treating heart failure in a subject having or at risk for heart failure who is or is at risk of being intolerant to treatment with a renin-angiotensin-aldosterone system (RAAS) inhibitor, comprising administering about 15 mg to about 200 mg of an oligomeric agent or salt thereof to a subject having or at risk for heart failure, wherein the oligomeric agent comprises a modified oligonucleotide consisting of 16-30 linked nucleosides, and wherein the modified oligonucleotide comprises a nucleobase sequence of at least 16 contiguous nucleosides at least 80% complementary to the nucleobase sequence of an equal length region of nucleobases 2046-2061 of SEQ ID NO: 1 or nucleobases 14940-14955 of SEQ ID NO: 2; and wherein the amount of AGT RNA and/or AGT protein in the subject is decreased by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent.

161. A method for reducing AGT RNA and/or AGT protein in a subject, comprising administering 60 mg to 120 mg of an oligomeric agent or salt thereof to a subject having or at risk for heart failure with reduced ejection fraction (HFrEF); wherein the oligomeric agent comprises a modified oligonucleotide consisting of 16-30 linked nucleosides, and wherein the modified oligonucleotide comprises a nucleobase sequence of at least 16 contiguous nucleosides at least 80% complementary to the nucleobase sequence of an equal length region of nucleobases 2046-2061 of SEQ ID NO: 1 or nucleobases 14940-14955 of SEQ ID NO: 2; and wherein the amount of AGT RNA and/or AGT protein in the subject is decreased by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent.

162. Use of an oligomeric agent or salt thereof for treating heart failure in a subject having or at risk for heart failure who is or is at risk of being intolerant to treatment with a renin-angiotensin-aldosterone system (RAAS) inhibitor, wherein:

the oligomeric agent comprises a modified oligonucleotide consisting of 16-30 linked nucleosides, wherein the modified oligonucleotide comprises a nucleobase sequence of at least 16 contiguous nucleosides and wherein the modified oligonucleotide is at least 80% complementary to the nucleobase sequence of an equal length region of nucleobases 2046-2061 of SEQ ID NO: 1 or nucleobases 14940-14955 of SEQ ID NO: 2, or salt thereof to a subject having or at risk for heart failure; and

wherein the oligomeric agent decreases the amount of AGT RNA and/or AGT protein in a subject by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent.

163. Use of an oligomeric agent or salt thereof in the manufacture of a medicament for reducing the amount of AGT RNA and/or AGT protein in a subject or for treating heart failure and/or ameliorating one or more symptoms of heart failure, wherein:

the oligomeric agent comprises a modified oligonucleotide consisting of 16-50 linked nucleosides, wherein the modified oligonucleotide comprises at least 13 contiguous nucleosides at least 80% complementary to the nucleobase sequence of an equal length region of nucleobases 2046-2061 of SEQ ID NO: 1 or nucleobases 14940-14955 of SEQ ID NO: 2; and

the oligomeric agent decreases the amount of AGT RNA and/or AGT protein in a subject by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent or salt thereof.

164. Use of 60 mg to 120 mg of an oligomeric agent or a salt thereof for reducing AGT RNA and/or AGT protein in a subject having or at risk for heart failure with reduced ejection fraction (HFrEF); wherein the oligomeric agent comprises a modified oligonucleotide consisting of 16-30 linked nucleosides, and wherein the modified oligonucleotide comprises a nucleobase sequence of at least 16 contiguous nucleosides at least 80% complementary to the nucleobase sequence of an equal length region of nucleobases 2046-2061 of SEQ ID NO: 1 or nucleobases 14940-14955 of SEQ ID NO: 2; and wherein the amount of AGT RNA and/or AGT protein in the subject is decreased by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent.

165. The method or use of any one of claims 159-164, wherein the subject has or is at risk for, or the heart failure is, heart failure with reduced ejection fraction (HFrEF), heart failure with mid-range ejection fraction (HFmrEF), heart failure with improved ejection fraction (HFimpEF), or heart failure with preserved ejection fraction (HFpEF).

166. The method or use of any one of claims 159-164, wherein the subject has a left ventricular ejection fraction of about 50% or less, about 40% or less, or about 35% or less, or about 30% or less.

167. The method or use of any one of claims 159-164, wherein the subject has one or more of asymptomatic left ventricular dysfunction (ALVD), asymptomatic or symptomatic valvular heart disease, left ventricular hypertrophy, left ventricular fibrosis, left ventricular dilatation, and left ventricular hypocontractility.

168. The method or use of any one of claims 159-167, wherein the amount of AGT protein in the liver of the subject is reduced.

169. The method or use of any one of claims 159-167, wherein the amount of AGT protein in the blood, serum or plasma of the subject is reduced.

170. The method or use of any one of claims 159-169, wherein a decrease in the amount of AGT RNA and/or AGT protein in the subject is less than 95%, or less than 94%, or less than 93%, or less than 92%, or less than 91%, or less than 90% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent or salt thereof.

171. The method or use of any one of claims 159-169, wherein the amount of AGT RNA and/or AGT protein in the subject is decreased by no more than 85%, or no more than 86%, or no more than 87%, or no more than 88%, or no more than 89%, or no more than 90%, or no more than 91%, or no more than 92%, or no more than 93%, or no more than 94%, or no more than 95% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent or salt thereof.

172. The method or use of any one of claims 159-169, wherein the amount of AGT RNA and/or AGT protein is decreased by at least 75%, at least 80% or at least 85% and less than 95% compared to the amount of AGT protein prior to administering the oligomeric agent or salt thereof.

173. The method or use of any one of claims 159-169, wherein the amount of AGT RNA and/or AGT protein is decreased by at least 70% or at least 75%, at least 80% or at least 85% and less than 90% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent or salt thereof.

174. The method or use of any one of claims 159-169, wherein the amount of AGT RNA and/or AGT protein in the subject is decreased by at least 70% or at least 75% and less than 95%, less than 94%, less than 93%, less than 92%, less than 91%, less than 90%, less than 89%, less than 88%, or less than 85% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent or salt thereof.

175. The method or use of any one of claims 159-174, wherein the nucleobase sequence comprises at least 13, at least 14, at least 15 or at least 16 contiguous nucleobases at least 85%, at least 90%, at least 95%, or 100% complementary to the nucleobase sequence of an equal length region of nucleobases 2046-2061 of SEQ ID NO: 1 or nucleobases 14940-14955 of SEQ ID NO: 2.

176. The method or use of any one of claims 159-174, wherein the nucleobase sequence comprises at least 13, at least 14, at least 15, or at least 16 contiguous nucleobases of any one of the nucleobase sequence of SEQ ID NOs: 3-5.

177. The method or use of any one of claims 159-174, wherein the modified oligonucleotide consists of 16 to 17, 16 to 18, 16 to 20, 16 to 25, 16 to 30, 17 to 20, 17 to 25, 17 to 30, 18 to 20, 18 to 25, 18 to 30, 19 to 20, 19 to 25, 19 to 30, 20 to 25, 20 to 30, 21-23, 21 to 25, 21 to 30, 22 to 25, 22 to 30, 23 to 25, or 23 to 30 linked nucleosides.

178. The method or use of any one of claims 159-174, wherein the modified oligonucleotide consists of 16 to 30 linked nucleosides and comprises or consists of a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 3-5.

179. The method or use of any one of claims 159-178, wherein the modified oligonucleotide comprises one or more i) modified nucleosides comprising a modified sugar moiety, ii) cyclic sugar surrogate, iii) acyclic sugar surrogate, iii) modified internucleoside linkage, and/or iv) modified nucleobase.

180. The method or use of claim 179, wherein the modified sugar moiety is a modified furanosyl sugar moiety or a sugar surrogate.

181. The method or use of claim 179, wherein the modified nucleoside comprises a bicyclic modified sugar moiety comprising a 4'-2' bridge selected from 4'-CH₂-O-2' and 4'-CH(CH₃)-O-2'.

182. The method or use of claim 179, wherein the modified nucleoside comprises a non-bicyclic modified sugar moiety selected from a 2'-MOE sugar moiety, 2'-OMe sugar moiety, a 2'-F sugar moiety, or a 2'-NMA sugar moiety.

183. The method or use of claim 179, wherein each internucleoside linkage of the modified oligonucleotide is independently selected from a phosphodiester internucleoside linkage, a phosphorothioate internucleoside linkage, and a mesyl phosphoramidate internucleoside.

184. The method or use of claim 179, wherein the modified nucleobase is 5-methylcytosine or hypoxanthine.

185. The method or use of claim 179, wherein each nucleoside of the modified oligonucleotide comprises a nucleobase.

186. The method or use of claim 179, wherein each nucleoside of the modified oligonucleotide is independently selected from a furanosyl nucleoside, a cyclic sugar surrogate nucleoside, and an acyclic sugar surrogate nucleoside comprising a nucleobase.

187. The method or use of claim 179, wherein at least one nucleoside of the modified oligonucleotide comprises an unmodified sugar moiety.

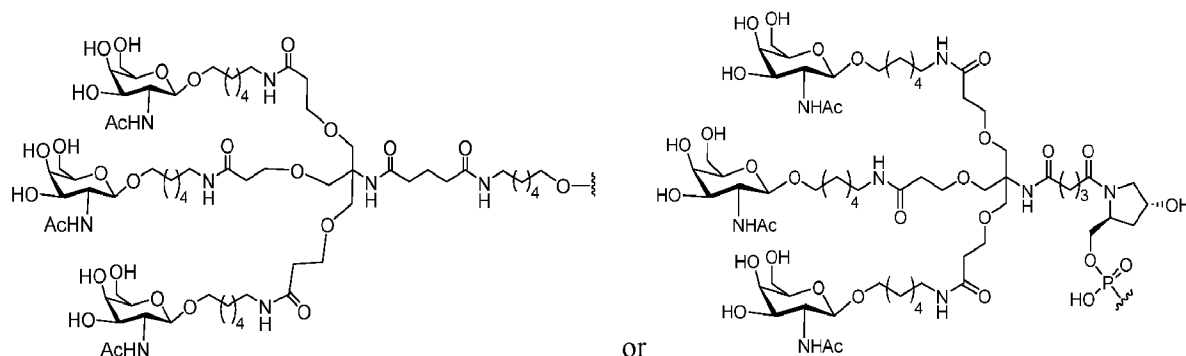
188. The method or use of claim 179, wherein at least one nucleoside of the modified oligonucleotide comprises an unmodified DNA sugar moiety.

189. The method or use of any one of claims 1-188, wherein the oligomeric agent or salt thereof comprises a conjugate group comprising a conjugate linker and a conjugate moiety comprising a cell-targeting moiety.

190. The method or use of claim 189, wherein the cell-targeting moiety comprises a moiety that interacts with or binds to a liver cell.

191. The method or use claim 190, wherein the conjugate group comprises a N-acetyl galactosamine (GalNAc) moiety.

192. The method or use of claim 191, wherein the conjugate group comprises the following structure:



193. The method or use of any one of claims 189-192, wherein the conjugate group comprises a conjugate linker consisting of a single bond and/or comprises a cleavable linker.

194. The method or use of any one of claims 189-193, wherein the conjugate group is attached to the 5'-terminal nucleoside or to the 3'-terminal nucleoside of the modified oligonucleotide.

195. The method or use of any one of claims 159-194, wherein the modified oligonucleotide comprises a deoxy region consisting of 5-12 linked nucleosides.

196. The method or use of claim 195, wherein the deoxy region consists of 6, 7, 8, 9, 10, or 6-10 linked nucleosides.

197. The method or use of claim 195 or claim 196, wherein each nucleoside immediately adjacent to the deoxy region comprises a modified sugar moiety.

198. The method or use of claim 196, wherein the deoxy region is flanked on the 5'-side by a 5'-region consisting of 1-6 nucleosides and on the 3'-side by a 3'-region consisting of 1-6 linked nucleosides; wherein the 3'-most nucleoside of the 5'-region comprises a modified sugar moiety and the 5'-most nucleoside of the 3'-region comprises a modified sugar moiety.

199. The method or use of claim 198, wherein each nucleoside of the 3'-region comprises a modified sugar moiety and/or wherein each nucleoside of the 5'-region comprises a modified sugar moiety.

200. The method or use of any one of claims 199, wherein each nucleoside of the 5'-region independently is a cEt nucleoside, a 2'-OMe nucleoside, or a 2'-MOE nucleoside and each nucleoside of the 3'-region independently is a cEt nucleoside, a 2'-OMe nucleoside, or a 2'-MOE nucleoside.

201. The method or use of any one of claims 195-200, wherein the modified oligonucleotide has a 5'-region consisting of 3 linked nucleosides, a deoxy region consisting of 6-10 linked nucleosides, and a 3'-region consisting of 1-6 linked nucleosides.

202. The method or use of any one of claims 195-200, wherein the modified oligonucleotide has a sugar motif (5' to 3') selected from: eekdddddskke, ekkdddddskke, kkkdydddddskk, kkkdydddddskk, kkkdydddddskk, kkkdddddskk, kkkdddddskk, or eeeedddddeeee; wherein 'e'

represents a 2'-MOE sugar moiety, 'k' represents a cEt sugar moiety, 'd' represents an unmodified DNA sugar moiety, and 'y' represents a 2'-OMe sugar moiety.

203. The method or use of any one of claims 159-202, wherein each internucleoside linkage of the modified oligonucleotide is independently selected from a phosphodiester internucleoside linkage and a phosphorothioate internucleoside linkage.

204. The method or use of any one of claims 159-202, wherein the modified oligonucleotide has an internucleoside linkage motif of soosssssssssos; wherein s is a phosphorothioate internucleoside linkage and o is a phosphodiester internucleoside linkage.

205. A method for reducing the amount of angiotensinogen (AGT) RNA and/or AGT protein in a subject who is or is at risk of being intolerant to treatment with a renin-angiotensin-aldosterone system (RAAS) inhibitor, comprising administering about 15 mg to about 200 mg an oligomeric agent or salt thereof to a subject having or at risk for heart failure, wherein the oligomeric agent comprises a modified oligonucleotide consisting of 16-30 linked nucleosides, and wherein the modified oligonucleotide comprises a nucleobase sequence of at least 16 contiguous nucleosides at least 80% complementary to the nucleobase sequence of an equal length region of SEQ ID NO: 1 or SEQ ID NO: 2;

wherein: the amount of AGT RNA and/or AGT protein in the subject is decreased by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent; and

wherein the subject has or is at risk for heart failure with reduced ejection fraction (HFrEF), heart failure with mid-range ejection fraction (HFmrEF), heart failure with improved ejection fraction (HFimpEF), or heart failure with preserved ejection fraction (HFpEF).

206. A method of treating heart failure in a subject having or at risk for heart failure who is or is at risk of being intolerant to treatment with a renin-angiotensin-aldosterone system (RAAS) inhibitor, comprising administering about 15 mg to about 200 mg of an oligomeric agent or salt thereof to a subject having or at risk for heart failure, wherein the oligomeric agent comprises a modified oligonucleotide consisting of 16-30 linked nucleosides, and wherein the modified oligonucleotide comprises a nucleobase sequence of at least 16 contiguous nucleosides at least 80% complementary to the nucleobase sequence of an equal length region of SEQ ID NO: 1 or SEQ ID NO: 2; and wherein the amount of AGT RNA and/or AGT protein in the subject is decreased by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent; and wherein the subject has or is at risk for heart failure with reduced ejection fraction (HFrEF), heart failure with mid-range ejection fraction (HFmrEF), heart failure with improved ejection fraction (HFimpEF), or heart failure with preserved ejection fraction (HFpEF).

207. Use of an oligomeric agent or salt thereof for treating heart failure in a subject having or at risk for heart failure who is or is at risk of being intolerant to treatment with a renin-angiotensin-aldosterone system (RAAS) inhibitor, wherein:

the oligomeric agent comprises a modified oligonucleotide consisting of 16-30 linked nucleosides wherein the modified oligonucleotide comprises a nucleobase sequence of at least 16 contiguous nucleosides and wherein the modified oligonucleotide is at least 80% complementary to the nucleobase sequence of an equal length region of SEQ ID NO: 1 or SEQ ID NO: 2, or salt thereof to a subject having or at risk for heart failure; and

wherein the oligomeric agent decreases the amount of AGT RNA and/or AGT protein in a subject by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent; and wherein the subject has or is at risk for heart failure with reduced ejection fraction (HFrEF), heart failure with mid-range ejection fraction (HFmrEF), heart failure with improved ejection fraction (HFimpEF), or heart failure with preserved ejection fraction (HFpEF).

208. Use of an oligomeric agent or salt thereof in the manufacture of a medicament for reducing the amount of AGT RNA and/or AGT protein in a subject or for treating heart failure and/or ameliorating one or more symptoms of heart failure, wherein:

the oligomeric agent comprises a modified oligonucleotide consisting of 12-80 linked nucleosides, wherein the modified oligonucleotide comprises at least 16 contiguous nucleosides at least 80% complementary to the nucleobase sequence of an equal length region of SEQ ID NO: 1 or SEQ ID NO: 2; and

the oligomeric agent decreases the amount of AGT RNA and/or AGT protein in a subject by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent or salt thereof; and wherein the subject has or is at risk for heart failure with reduced ejection fraction (HFrEF), heart failure with mid-range ejection fraction (HFmrEF), heart failure with improved ejection fraction (HFimpEF), or heart failure with preserved ejection fraction (HFpEF).

209. A method for reducing AGT RNA and/or AGT protein in a subject, comprising administering 60 mg to 120 mg of an oligomeric agent or salt thereof to a subject having or at risk for heart failure with reduced ejection fraction (HFrEF); wherein the oligomeric agent comprises a modified oligonucleotide consisting of 12-80 linked nucleosides, wherein the modified oligonucleotide comprises at least 16 contiguous nucleosides at least 80% complementary to the nucleobase sequence of an equal length region of SEQ ID NO: 1 or SEQ ID NO: 2; and wherein the oligomeric agent decreases the amount of AGT RNA and/or AGT protein in a subject by at least 70%, at least 75%, at least 80% or at least 85% and less than 95%

compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent or salt thereof.

210. Use of 60 mg to 120 mg of an oligomeric agent or a salt thereof for reducing AGT RNA and/or AGT protein in a subject having or at risk for heart failure with reduced ejection fraction (HFrEF); wherein the oligomeric agent comprises a modified oligonucleotide consisting of 12-80 linked nucleosides, wherein the modified oligonucleotide comprises at least 16 contiguous nucleosides at least 80% complementary to the nucleobase sequence of an equal length region of SEQ ID NO: 1 or SEQ ID NO: 2; and wherein the oligomeric agent decreases the amount of AGT RNA and/or AGT protein in a subject by at least 70%, at least 75%, at least 80% or at least 85% and less than 95% compared to the baseline amount of AGT RNA and/or AGT protein in the subject prior to any administration of the oligomeric agent or salt thereof.

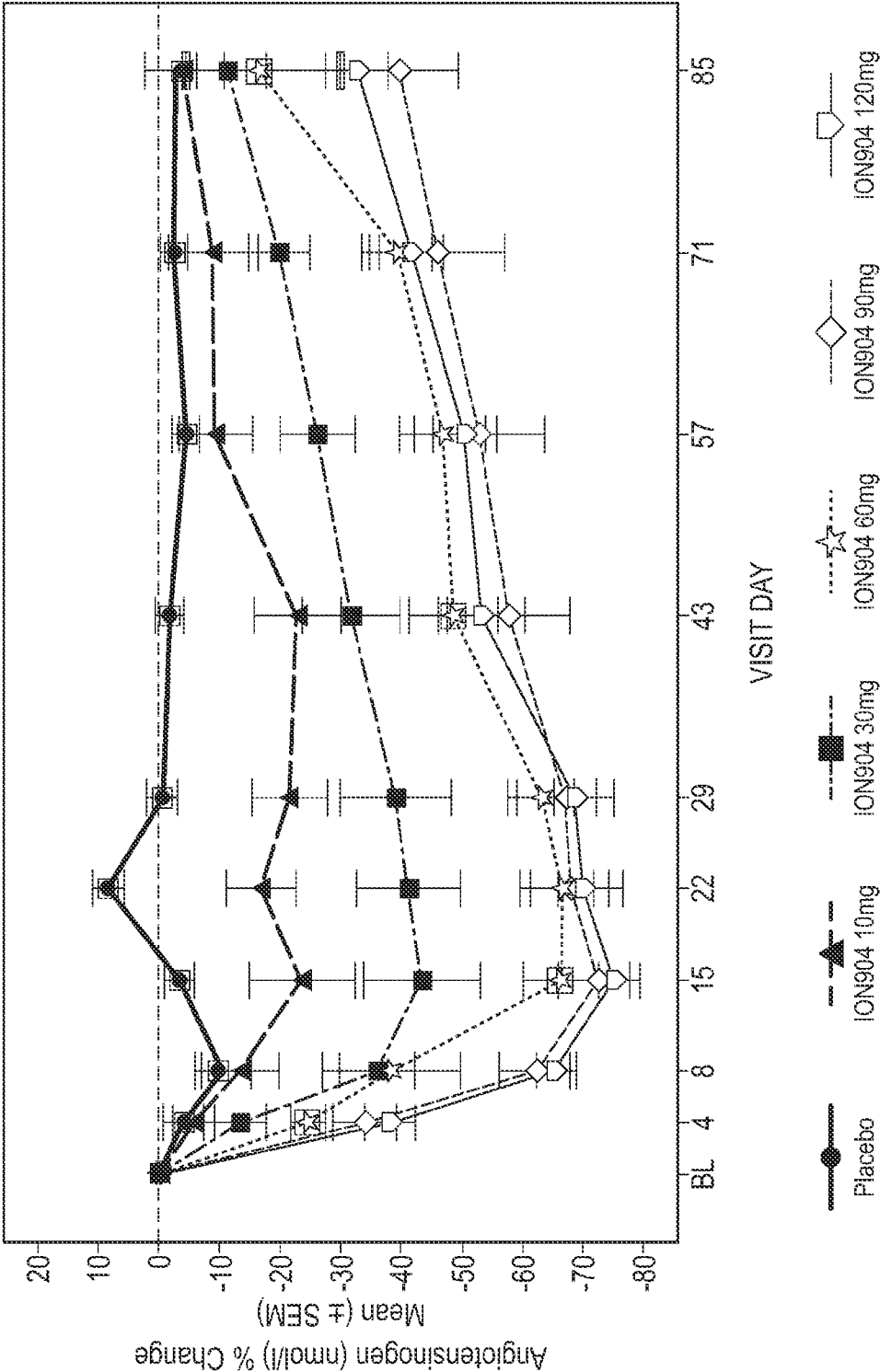


FIG. 1

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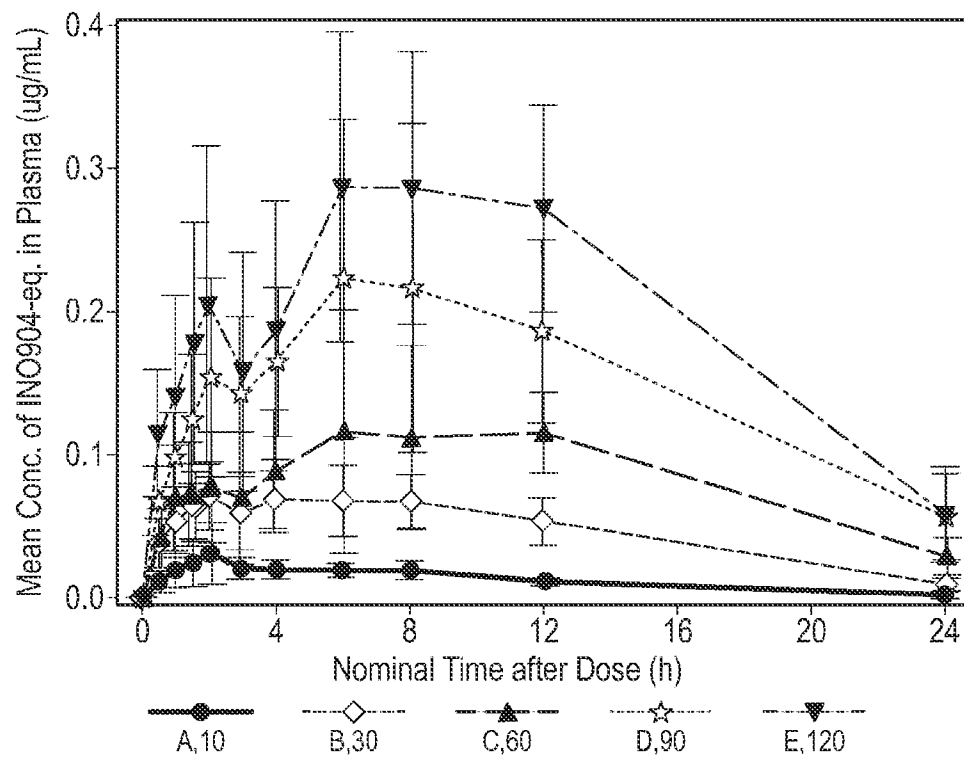


FIG. 2

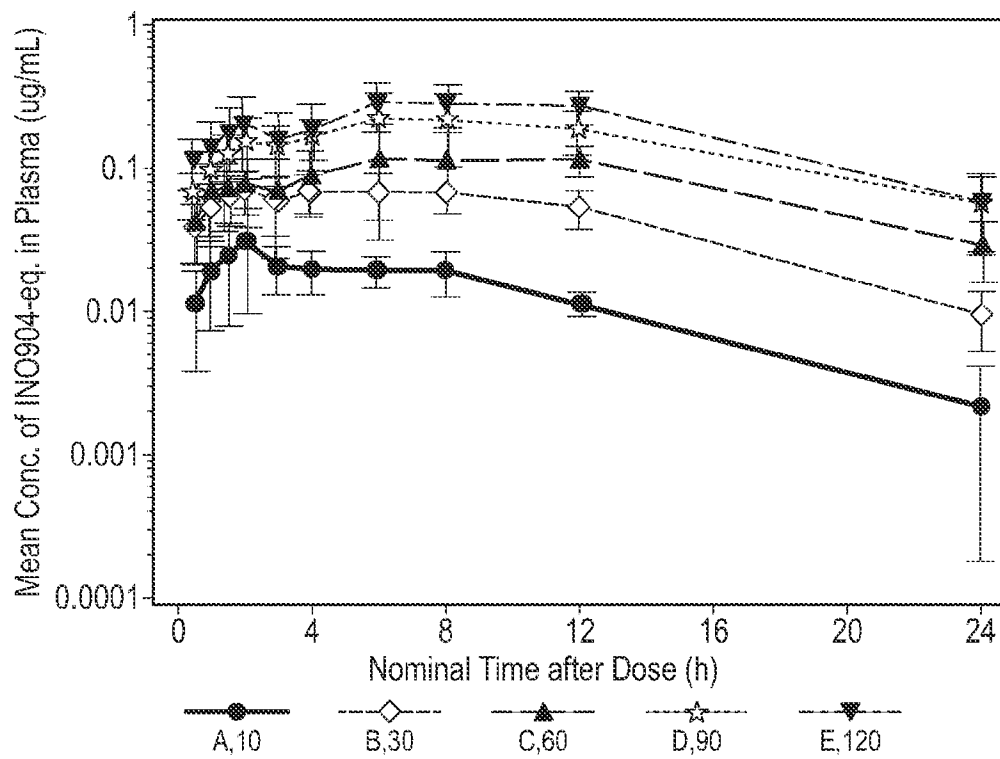


FIG. 3

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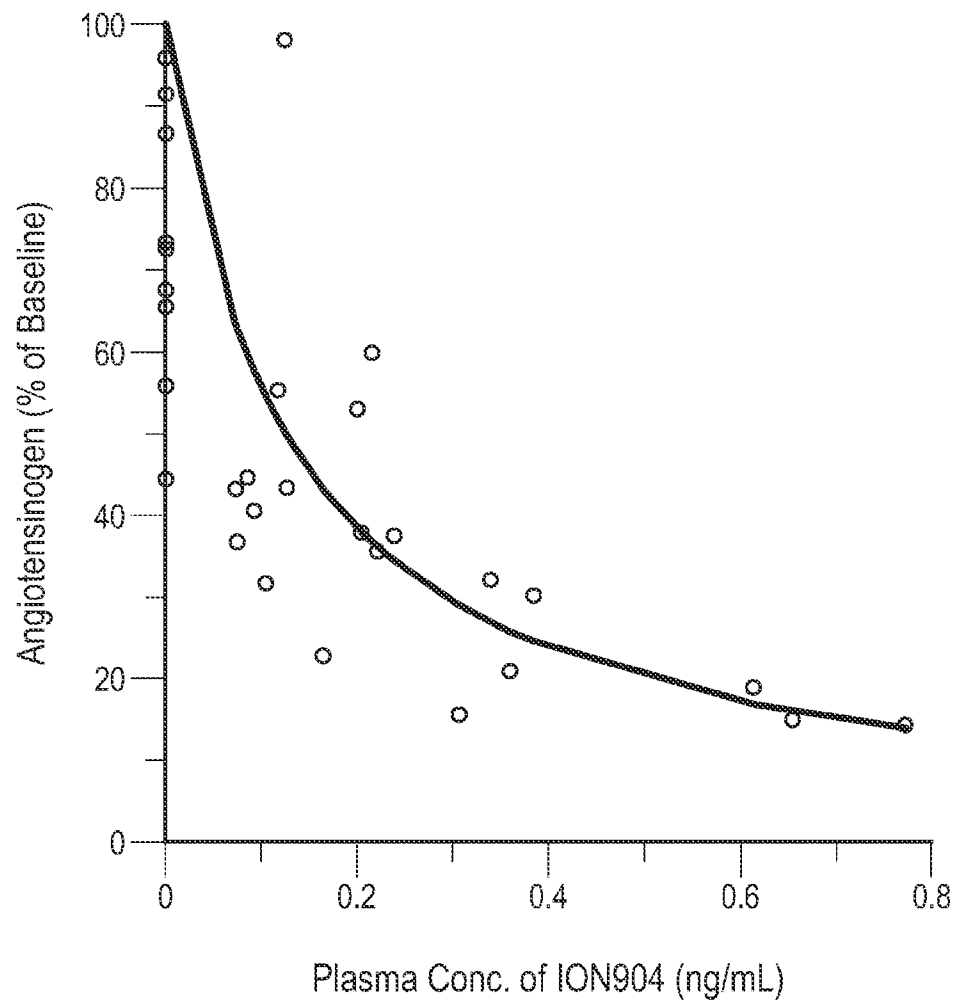
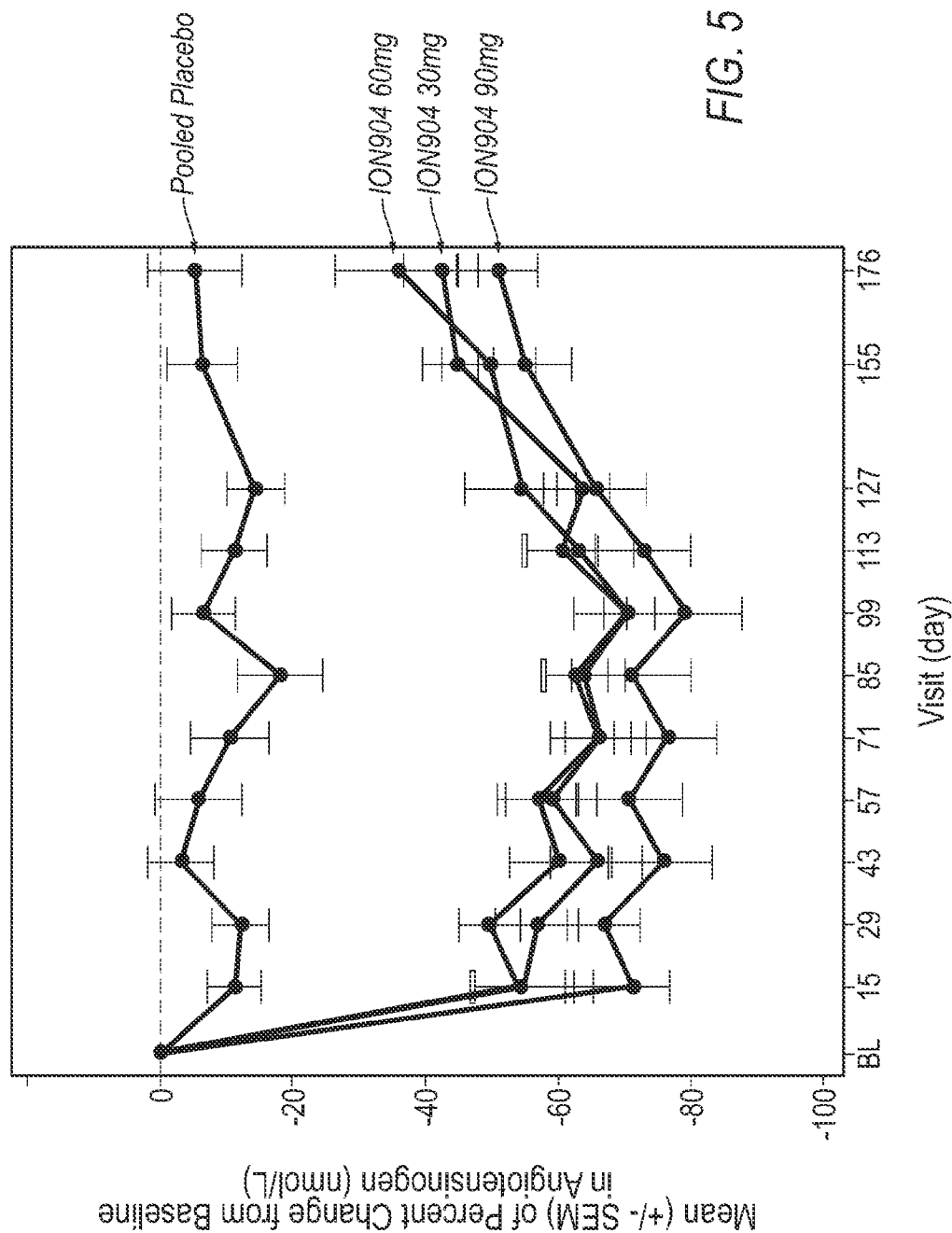


FIG. 4



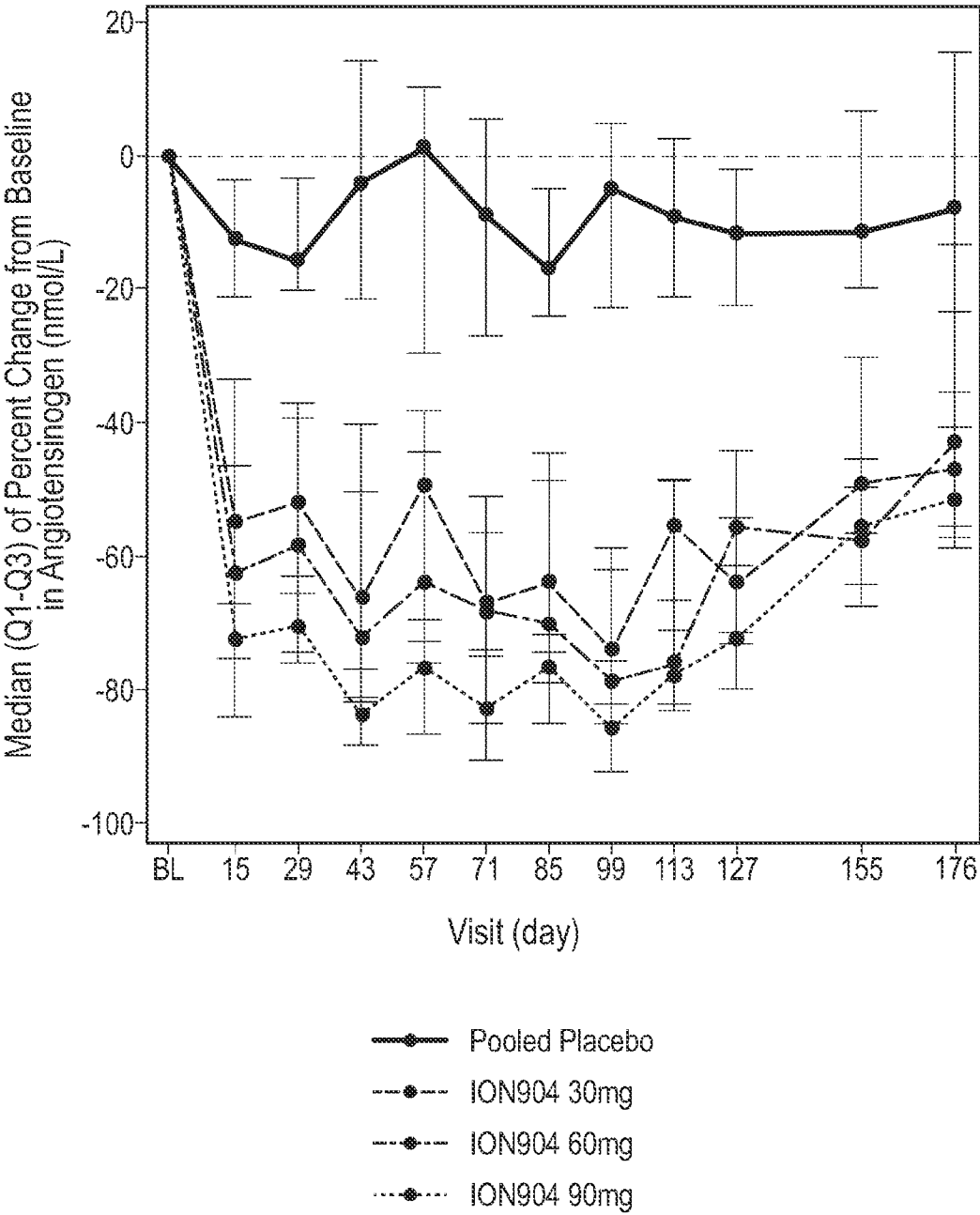


FIG. 6

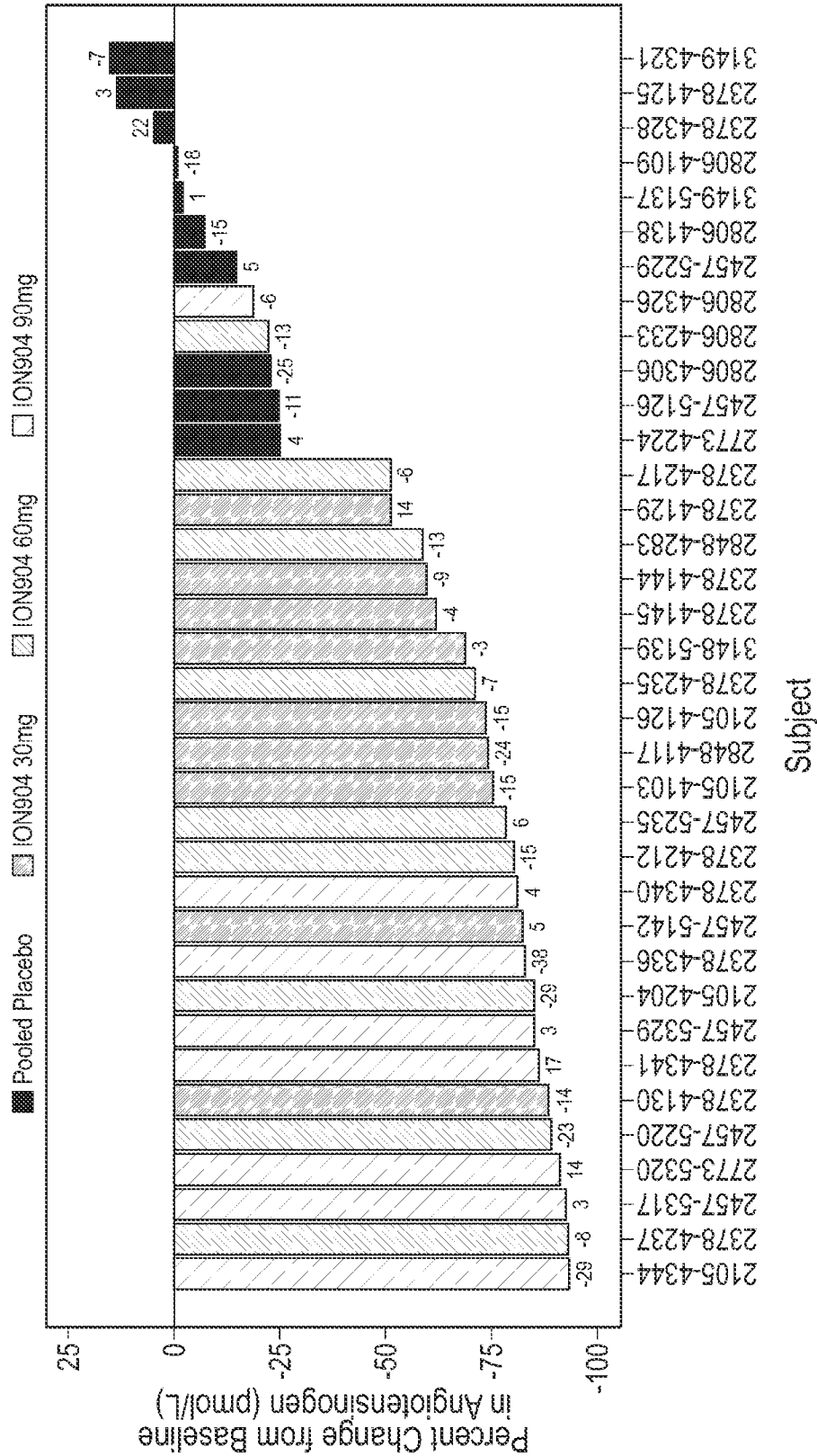


FIG. 7

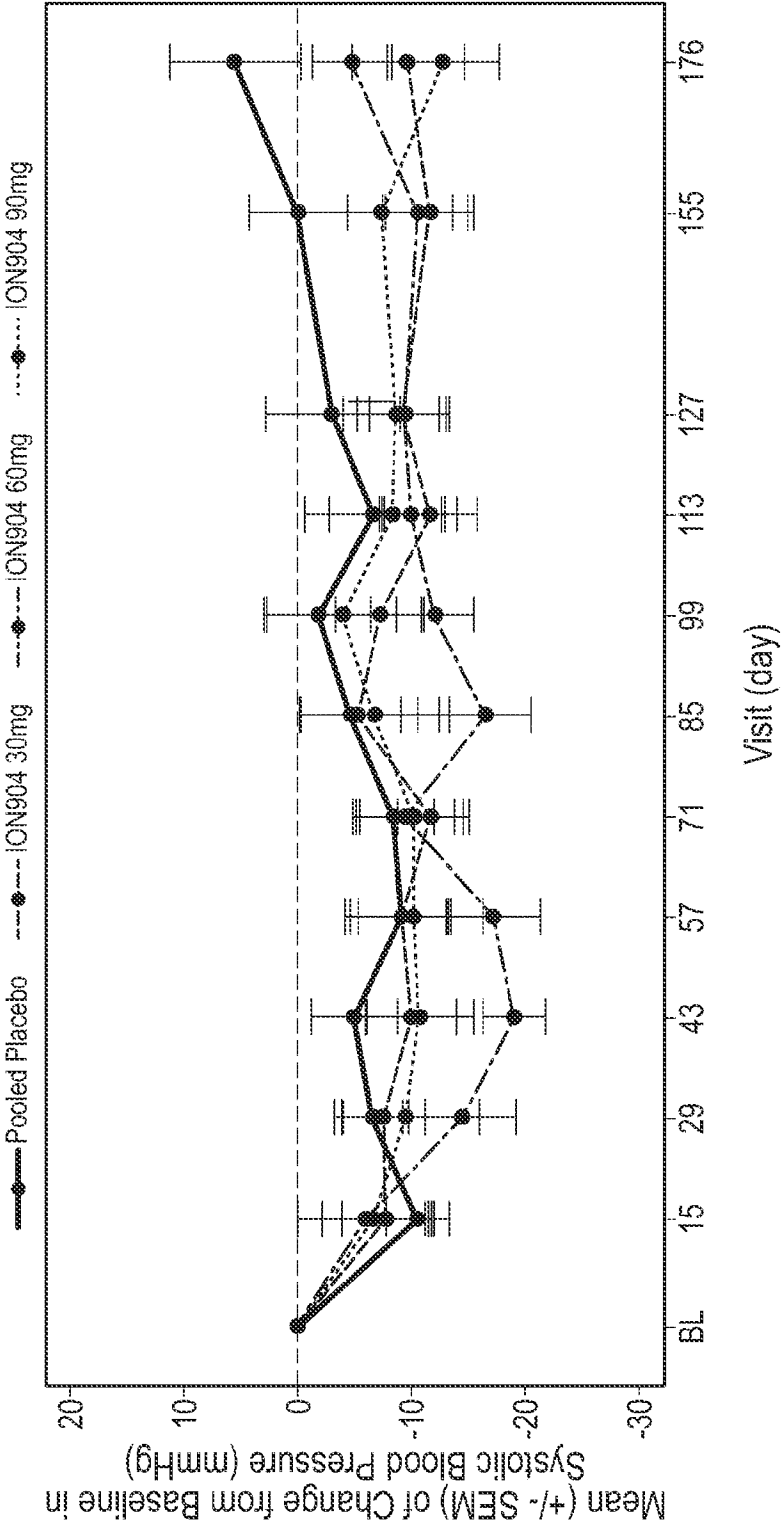


FIG. 8

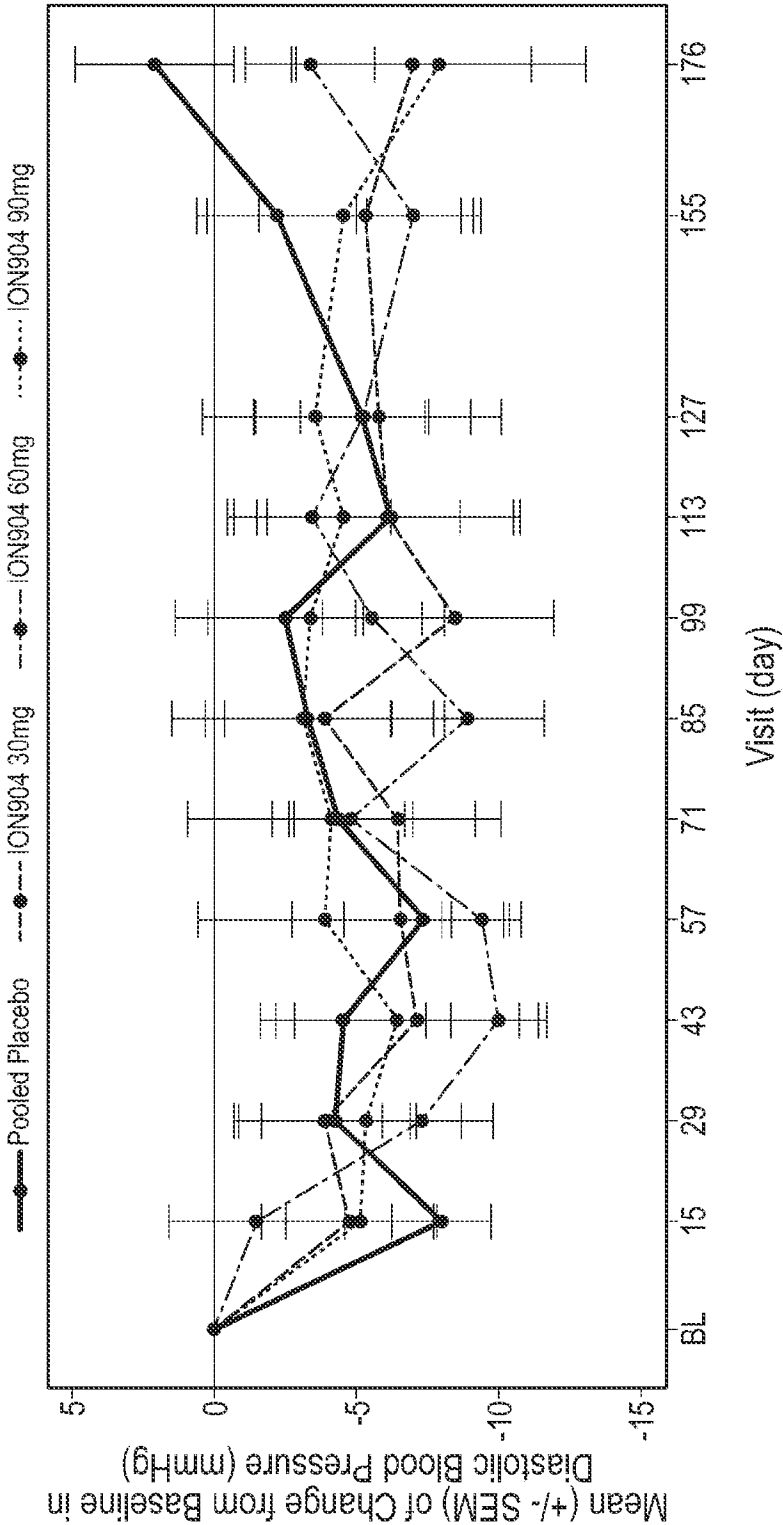


FIG. 9

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/054244

A. CLASSIFICATION OF SUBJECT MATTERIPC: **A61K 31/7088** (2024.01); *C07H 21/02* (2024.01); *C12N 15/113* (2024.01); *A61P 9/12* (2024.01)CPC: **A61K 31/7088**; *C07H 21/02*; *C12N 15/113*; *C12N 2310/346*; *A61P 9/12*

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	US 2022/0298200 A1 (Ionis Pharmaceuticals, Inc.) 22 September 2022 (22.09.2022) claim 1-2, abstract, para [0005], [0062], [0093], [0286], [0411]	1-6, 11-12, 14-16, 106-131, 157-160, 162-163, 167, 210
Y	claim 1-2, abstract, para [0005], [0062], [0093], [0286], [0411]	7-10, 161, 164-166, 205-209
A	US 2021/0310006 A1 (Alnylam Pharmaceuticals, Inc.) 07 October 2021 (07.10.2021) entire document	1-12, 14-16, 106-131, 157-167, 205-210
A	WO 2023/278576 A1 (ALNYLAM PHARMACEUTICALS, INC.) 05 January 2023 (05.01.2023) entire document	1-12, 14-16, 106-131, 157-167, 205-210



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

23 December 2024 (23.12.2024)

Date of mailing of the international search report

13 January 2025 (13.01.2025)

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/054244

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.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.1(a)),
☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/054244

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.: **13, 17-105, 132-156, 168-204**
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/054244

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2022/0000901 A1 (Ionis Pharmaceuticals, Inc.) 06 January 2022 (06.01.2022) entire document	1-12, 14-16, 106-131, 157-167, 205-210
Y	Stolfo et al. "Use of Renin–Angiotensin–Aldosterone System Inhibitors in Older Patients with Heart Failure and Reduced Ejection Fraction" Cardiac Failure Review. 24 May 2019, vol 24, pg. 70-73 pg. 70, abstract	7-10, 161, 164-166, 205-209